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EXCITATION AND INHIBITION IN EPILEPSY[1]

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ADMIRABLE in Hughlings Jackson's papers is his pithy way of telling a clinical story with running commentary of interjection and footnote. In his Lumleian Lectures (Jackson, 1931) he presents a case of local epilepsy in what he calls a drama of four acts. In the opening scene "A man, B., was seemingly quite well when he arrived at my house after a walk of about a mile." In the second act a fit begins in the toes of the left foot. Of the first act Jackson remarks: "The patient was not really well when he arrived at my house. He had a persistent discharging lesion, presumably in a few cells of his leg centre; so to say, he always carried it about with him, or, to speak more precisely, it was a persistent, quasi-parasitical, hyperfunctionable part of himself." This was indeed what he meant. Elsewhere he says: "The discharging lesion is a local, persisting, hyperphysiological state of nerve cells induced by some pathological change," and again, "These discharges are to be looked upon as gross exaggerations of healthy nervous discharges." As to the form this exaggeration might take he remarks in a later paper, "I do not mean that 'nerve impulses' after discharges which produce convulsion travel faster than those after discharges of health, but that in the former case more numerous 'nerve impulses' are emitted in a given time, or else that more nerve cells are simultaneously discharging." Translated into terms of electrically recorded potentials these hypotheses are now seen to be correct, which is an indication both of Hughlings Jackson's imaginative genius and of his influence upon the form of neurophysiology as we know it today.

There are many questions about epilepsy to which there is still no satisfactory answer. What is the basis of the persistent discharging lesion such as Jackson's patient carried about with him? I do not, of course, mean to ask whether the patient had a tumour or a scar, but how such a tumour or scar causes a liability to seizures. Again, what is it

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that determines the onset of a seizure in a person carrying this liability? And once the seizure has begun what determines its cessation? To all these questions Jackson, and many others who have followed him, have devoted a great deal of thought yet they are perhaps worth reconsideration at the present time in the light of recent physiological and biochemical research. Setting aside the first question for the moment, let us consider what clinical observation may have to tell us about the excitation or inhibition of seizures.

Clinical Observation

The observation that in some cases an epileptic seizure might be provoked by physiological or psychical stimuli is an old one. Evoked seizures—a better term than reflex epilepsy—were recognized by Jackson (1925) and fully described by Gowers (1901). An excellent account of the subject is given by Allen (1945). I have found them described in 65 out of 1,000 consecutive patients presenting in my consulting-room with the complaint of epileptic seizures, but am convinced from retrospective analysis that other examples might have been discovered by proper enquiry. Precipitation by a particular stimulus in certain cases may be observed only in a small proportion of the seizures and may be omitted from the story, and in some instances the nature of the stimulus is such that it may easily escape notice. This until a few years ago was true for flickering light, now recognized as a common precipitant of *petit mal*. The element of flicker is, however, not essential and abrupt transition from darkness to light may evoke a seizure. The converse may also obtain. Two of my patients had attacks with a sudden change from light to darkness, as when entering a cinema. One of these almost always had a minor seizure within a second or two of closing her eyes when going to sleep, and her clothes had to be made especially loose to prevent exposure to darkness when dressing or undressing. It is evident, therefore, that the "off" as well as the "on" signal from the retina may be effective. This may also be true for hearing. In one of my cases there was a particular liability for seizures to occur at moments of sudden transition from noise to unexpected silence.

It is well known that the visual or auditory stimulation required to excite a seizure may be of a complex kind. The act of reading provides a striking example and was clearly described by two of my patients though it is only in the past three years that "reading epilepsy" has become widely recognized (Bickford and others, 1956; Chavany and others, 1956; Bingel, 1957; Stevens, 1957). In one of my patients writing was said to cause attacks, and I was able to witness a seizure thus precipitated. A comparable case was recorded by Gordon (1928). On the auditory side musicogenic epilepsy has long been known (Critchley, 1937), and there are other complex variants.

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There are also cases in which a particular movement may evoke seizures, especially, as Gowers noted, movement after rest—getting out of a chair quickly or turning over in bed.

Precipitation of attacks by visceral stimuli is, I suspect, more common than has generally been supposed. When the association is constant it is easily recognized. For example, a man who had occasional major attacks in his sleep was also liable to minor seizures in the day, taking the form of sudden confusion and a sense of familiarity lasting two or three minutes. These never occurred except when he was eating and only towards the end of a heavy meal. The bigger the meal and the more quickly it was eaten the more likely he was to have an attack. Having become aware of this, he took care to avoid gastric distension and was thus able to avoid attacks, but on a recent occasion was obliged to eat a rushed meal, got a feeling of gastric distension and was unable to bring up wind (a procedure which had been previously effective in preventing an attack). He then had the usual aura, this time followed by a major seizure. Another patient also had his minor attacks only when eating and only after he had eaten a good deal. "If," he said, "I eat slowly and read they never happen." A comparable case is recorded by Allen (1945). Working backwards from these cases in which the association was invariable I have noted others in which attacks have occurred more often during meals than appeared likely from coincidence. Such observations illustrate the complex nature of the effective stimulus in certain cases and the consequent need for close interrogation before it is decided that there is no precipitating cause for epileptic seizures.

I shall refer only in passing to other and well-known stimuli that may evoke seizures—startle, sudden noise, painful or tactile stimulation, or a burst of anger, for example. It is also recognized that the evocation of seizures may be conditioned as in the case of a patient who learned to produce attacks in himself by looking at a safety-pin (Mitchell, Falconer and Hill, 1954).

In some cases of evoked epilepsy the activity or stimulation is effective only if prolonged for some time. Reading epilepsy is one example. The seizure does not occur when reading is begun but only after several minutes and sometimes only after two or three hours. Auditory stimulation also may need to be repeated or prolonged to evoke seizures. Critchley (1937) records a case in which attacks would develop if the patient heard a noise of a continued or monotonous order, such as machinery in a workshop or a kettle on the boil, and in one of my own patients reiterative noise such as a frog croaking or a cat mewing would precipitate seizures. In both instances the auditory stimulus had to continue for some time before the fit developed. The prolonged exercise of a particular mental activity may also be responsible. Playing chess in one of my patients and adding figures in another were very likely to

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end in an attack. In a case reported by Bingel (1957) seizures occurred after playing cards for any time longer than two hours.

That a chronic state of peripheral excitation may cause an increased liability to seizures appeared true in a patient who proved to have a right parasagittal meningioma. Twenty-three years before the onset of his seizures his left leg had been amputated below the knee. The attacks at first took the form of clonic twitching limited to the muscles of the stump, lasting a minute or two, and continued thus at the rate of one every two or three days for a year. The seizures then gradually altered in that the twitching would extend at first to the thigh, then to the abdomen and finally to the arm, and eventually he had an attack in which he lost his senses. During the two years in which he had been subject to the minor attacks he had accepted the opinion that his symptoms were due to irritation in the stump, though he himself had not been aware of any new or abnormal sensation in it. He had therefore removed his artificial limb whenever convenient during the day as well as at night, and had never experienced a seizure when it was off. I have assumed in this case that afferent impulses, which were always present but of which he was unaware, and which on arrival at his cortex had no effect under normal conditions, were a contributory cause of epileptic seizures when the tumour was present. If we assume that of all the afferent stimuli reaching the brain only a comparatively small fraction are perceived, the number of cases in which seizures may be observed by the subject to be evoked by stimulation may be significant.

The arrest of a seizure after it has begun by means of some mental or bodily activity or a particular stimulus must be assigned to an inhibitory process. It has been many times described and in its simplest form is not uncommon. I have found it recorded in 53 out of the 1,000 cases already mentioned. In 25 instances it was stated that the attack could at times be cut short by some kind of mental effort. Most of these patients could not describe the occurrence better than to say that by pulling themselves together or an effort of concentration they were able to snap out of it. But in 8 cases a description was volunteered of a deliberate switch of mental attention. For example, one patient with an aura of noise said, "I may at this stage be able to jump my thoughts about and stop it." Another, whose attacks began with a sudden faraway feeling, a nice sort of feeling, said, "If I don't think about it it's all right, but if I say 'Oh, oh, look out, be careful' my mind automatically goes that way and I'm out." A patient who was himself a doctor and recognized his minor seizures, which consisted of a sudden feeling at the back of the nose going on to a disturbance of thought, stated, "By an effort of concentration I can always fight it off, but on one occasion I thought 'How will it develop?' and at once lost my senses." On this occasion he had a major seizure.

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The arrest of focal seizures by local stimulation of some kind was described by 12 of my patients and is so well known that the symptoms need not be described in detail.

The inhibitory process involved in arrest of seizures may be subject to the establishment of conditioned reflexes as in the remarkable case described by Efron (1956, 1957).

Physiology

Although it is now more than twenty years old the observation of self-sustained after-discharge of electric potentials in the cortex following electrical stimulation deserves first consideration, for the pattern and sequence of events correspond closely with those observed in a convulsive seizure, whether excited electrically or occurring as the result of disease. Cortical after-discharge following electrical stimulation, therefore, may be regarded as the counterpart of a subclinical seizure. Of especial interest is the manner in which the after-discharge ceases. Having continued for a time at a regular frequency of about 10 to 14 per second, the spikes then grow larger, and appear in groups with pauses in between. These pauses become gradually longer up to $\frac{1}{2}$ second or more, until the after-discharge ceases. Following this, if the potentials of the after-discharge have been very large, the whole area may be left inexcitable as well as inactive for 10 to 20 seconds. These observations are quoted from the classic paper of Adrian (1936), suggesting in his words "a conflict between a process by which each wave makes the system more unstable and an opposing process which causes a slower and slower recovery and ultimately stops all activity for many seconds." This process, he remarked, might be an inhibition, an accumulation of waste products or an exhaustion of active material, "though if it is an exhaustion it must be one which affects every neurone—even those which have only come into action at the height of the after-discharge." This objection to the hypothesis of exhaustion has never been answered. No evidence has been brought forward to sustain the hypothesis of waste products. The possibility of an inhibitory process remains and has received some support from the observations of Rosenblueth and Cannon (1942). If the state of inexcitability and inactivity immediately following the cessation of discharge represents inhibition it is inhibition of a degree which is not found under normal conditions, and we may deduce that an abnormal state of excitation has in its turn evoked an abnormal state of inhibition.

We must next consider the observations of Eccles (1957) and his collaborators, derived from recording with the micro-electrode the potentials within single motoneurones. They have demonstrated two different types of potential, the excitatory post-synaptic potential (E.P.S.P.) and the inhibitory post-synaptic potential (I.P.S.P.), each obtained by an appropriate mode of peripheral stimulation. These

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potentials result from the flux of ions across the cell membrane, the flow being governed by changes in the permeability of the membrane, which again are determined by the effect upon the membrane of excitatory and inhibitory transmitter substances. The change of potential, therefore, whether a depolarization (E.P.S.P.) or a hyperpolarization (I.P.S.P.) records in electrical terms the culmination of a series of chemical events. Arising from these and related studies there are several observations of especial interest to the student of epilepsy. The first is the discovery that within the spinal cord the motoneurone gives off a collateral branch forming a synapse with a Renshaw cell, which in turn makes synaptic connexions with motoneurones. It has been demonstrated that the function of the Renshaw neurone is strictly inhibitory. Thus each time the motoneurone develops an axon potential it excites an inhibitory impulse to motoneurones. Excitation evokes inhibition.

Phillips (1956*a*, 1956*b*) has applied the micro-electrode method to Betz cells in the cat and has discovered waves of hyperpolarization occurring not only as a sequel of excitatory activity in the cell but as independent happenings. He has further shown (Phillips, 1959) that inhibitory as well as excitatory effects can be produced in a Betz cell by antidromic stimulation of pyramidal fibres in the medulla other than the axon of the cell under observation by the micro-electrode. He has referred in this connexion to the long-established anatomical observation that the Betz cells give rise to axon collaterals ending on short interneurones which form synapses with Betz cells, an arrangement so like that of the axon collateral of the motoneurone to the Renshaw cell that it seems possible that, as in the spinal cord so in the cortex, the motor cell each time it discharges an axon potential excites an inhibitory interneurone to discharge a volley of impulses aimed at itself and its neighbours—a feedback system, which, as Phillips remarks, would be important in tending to prevent convulsive activity.

If we assume that there are inhibitory neurones in the cortex the recent observations of Eccles (1957) and his collaborators on the action of strychnine upon the motoneurone become important in relation to the effect of this substance in producing focal epileptic activity when applied to the cortex. These workers have shown that strychnine has no direct effect upon the excitatory post-synaptic potential of the motoneurone in reflex excitation, but causes a great diminution of the expected inhibitory post-synaptic potential provoked by an appropriate stimulus. Eccles suggests that strychnine acts by competing with the inhibitory transmitter substance for the appropriate receptor patches on the sub-synaptic membrane, and speaks of it as the curare of the inhibitory synapse. If this should be true for cortical cells we should have the answers to a number of questions, but at the same time further questions to be answered. If the epileptic activity produced by strychnine is caused by

a defect of inhibition whence comes the excitation? It may arise from afferent stimuli which would under normal conditions be inhibited and then have no electrical or clinical effect. It was long ago observed that if strychnine was applied to the motor cortex in a weak enough solution and for a short enough time convulsive activity was absent, but could be evoked by a sensory stimulus aimed at the appropriate area of cortex. Another answer to the same question might be that the resting activity of cortical cells may amount to convulsive activity when the inhibitory brakes are out of action. The effect of strychnine, on this hypothesis, would be satisfying for the clinician in that it offers the possibility of a persistent discharging lesion in the Jacksonian sense, which may be clinically subliminal except when some combination of stimuli, in space and time, evokes local excitation, stimuli of a kind and degree that would have caused no perceptible effect had it not been for the absence of inhibitory tone.

Relevant to the excitation of seizures by sensory stimuli are observations arising from the question raised by Adrian (1954) whether the afferent messages which can evoke sensation are allowed at all times to reach the cerebral cortex or are sometimes blocked at a lower level. There is now evidence recently reviewed by Dawson (1958) suggesting the existence of tonic activity descending from the cortex, and probably from the brain-stem and cerebellum, having an inhibitory effect at synapses on the afferent pathways. If it is accepted that the afferent inflow to the cortex is thus subject to continuous inhibitory control what might happen if this control were withdrawn? Dawson (1947*a*, 1947*b*) had previously observed in certain patients subject to myoclonic seizures which could be provoked by sensory stimulation, that a sensory stimulus applied to the periphery led to an electrical response recorded from the scalp over the sensory area which was many times larger than that found in healthy people. These observations raise the possibility that depression of inhibitory control resulting from cerebral disease might cause a pathological increase in the size of an afferent volley, which in its turn could be a factor in the excitation of epileptic discharge. Further studies on the unanæsthetized cat by means of implanted electrodes (Hernandez-Peón and others, 1957) suggest that inhibition of afferent inflow may be selective, and its direction governed by attention, so that, for example, impulses set up in the visual pathways by photic stimulation are depressed when the animal is at the same time exposed to an auditory or olfactory stimulus. If a change in the direction of attention can thus selectively inhibit afferent inflow, and if, as has been suggested, the evocation of epileptic discharge may sometimes depend upon a particular stimulus pattern, the effect of a deliberate switch of attention in arresting certain seizures might thus be explained.

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Biochemistry

The biochemical factors in epilepsy must be of primary importance. The abnormalities of electric potential associated with seizures are as much an effect of ionic flux across the cell membrane as is convulsive movement, and neither can give us any direct knowledge of the essential nature of the discharging lesion. It is natural that the identification of excitatory and inhibitory transmitter substances within the central nervous system should have been the centre of attention. So far the only one that is known is acetylcholine, which acts at the synapse of the axon collateral of the motoneurone with the Renshaw cell, and the question whether acetylcholine operates as a transmitter in the brain has been actively pursued. There is experimental evidence suggesting that acetylcholine plays a part in some epileptic seizures (Feldberg, 1957).

Another interesting line of enquiry began with the discovery by Florey (1954) that an extract of mammalian brain or spinal cord had an inhibitory effect upon the stretch receptor of the crayfish. This organ when subjected to moderate continuous stretch sends impulses up the afferent nerve at a frequency varying with the strength of the exciting stimulus. When the preparation is immersed in a solution containing small amounts of Florey's inhibitory, or I Factor, these impulses cease and return as soon as the solution has been washed off. The I Factor has since been identified as γ-amino-butyric acid (GABA) (Bazemore, Elliott and Florey, 1957). The effects of topical application of GABA to the cortex have now been studied in some detail (Purpura and others, 1957; Iwama and Jasper, 1957), and it is agreed that it abolishes the surface negative response to direct cortical stimulation with the appearance in its stead of a surface positive wave. Its effect upon potentials evoked in the cortex by stimulation of the sensory nucleus of the thalamus is to abolish the surface negative element of the normal diphasic response with an apparent small increase in the surface positive component. Whether the surface negative component has its origin in the apical dendrites, or in independent superficial neurones, is uncertain, but in either case it is assumed to be the effect of synaptic excitation. GABA therefore appears to block excitation in the superficial layer of the cortex, and unmask inhibition, and its action thus resembles, but is opposite to, that of strychnine. It is therefore not surprising that it has been found that oral premedication with GABA will protect animals against convulsions artificially induced by chemical means (Hawkins and Sarett, 1957).

GABA is present in considerable quantity in the brain, being formed in situ from glutamic acid by the catalytic effect of an enzyme which requires as co-enzyme pyridoxal phosphate. This is of interest as it has long been known that one of the symptoms resulting from pyridoxine deficiency in animals is epilepsy. Of further interest have been clinical

observations reported from the U.S.A. The first of these concerned the case of an infant in whom constant and intractable convulsions began three hours after birth (Hunt and others, 1954). The child was admitted to hospital at the age of two weeks and the history contained the observation that there had been two brief periods of freedom following an injection of a proprietary vitamin compound. This was confirmed, and by analysis and the process of elimination it was proved that the anticonvulsant factor in the compound was pyridoxine. It was then found that a daily dose of 2 mg. of pyridoxine orally controlled the seizures absolutely so that there was no recurrence except when the dose was omitted. In this case, therefore, there appears to have been an inborn error of metabolism, possibly familial, as a sibling had begun to have convulsions four hours after birth and died at the age of 30 hours. Comparable cases have since been reported (Bessey and others, 1957). Another observation was that of a widespread epidemic throughout the U.S.A. of generalized seizures in infants, beginning between the ages of 2 to 4 months and usually occurring several times a day. It eventually transpired that all these infants had been artificially fed and that the food they had been given was a particular brand of liquid milk substitute. When they were fed with another brand of milk substitute the seizures ceased. Analysis of the responsible milk substitute showed a gross deficiency of pyridoxine content as compared with similar preparations, this being due to a new method of sterilization which involved excessive heating. The preparation was withdrawn from the market and the epidemic ceased (Moloney and Parmelee, 1954; Coursin, 1954, 1956).

These observations suggest that GABA may be a natural anticonvulsant, present and formed in the brain, and that, when its production from glutamic acid is obstructed by pyridoxine deficiency, epilepsy is one of the results, at any rate in infants. From the evidence at present available it would appear that GABA is not an inhibitory transmitter substance, but that it blocks excitation, and that this effect is not confined to the sub-synaptic inhibitory areas but extends to the whole somadendritic membrane (Kuffler and Edwards, 1958). Elliott (1958) suggests that GABA exists in the interstitial fluids and exerts continuous effects on neuronal activity.

Reverting to the stretch receptor organ of the crayfish, we find another observation that may be relevant to an old-standing problem. Elliott and Florey (1956) have found that picrotoxin and metrazol do not obviously affect the activity of the stretch receptor neurone, but that both substances prevent the inhibitory effect on the preparation of relatively high concentrations of Factor I or GABA. Strychnine does not show this effect. Picrotoxin and metrazol in high dosage are convulsants in the crayfish, while strychnine is not. In fact the potencies of picrotoxin and metrazol as convulsants in the crayfish are roughly inversely

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proportional to the concentrations of these drugs required to prevent the action of Factor I. It has further been observed in mice that seizures induced by metrazol can be prevented by oral premedication with GABA (Hawkins and Sarett, 1957). We may here have a clue to the convulsant action of metrazol in man for which there has never been any satisfactory explanation.

Other recent observations that may be relevant to epilepsy are those upon the nature and functions of the blood-brain barrier (Bakay, 1956). Most substances when injected into a vein or into the peritoneum in animals penetrate the brain slowly and are thus found later and in smaller quantity than in other organs. Moreover, having gained entry to the brain, they are equally slow to pass the barrier in the other direction. The blood-brain barrier, as Tower (1958) has remarked, "functions as a homoeostatic mechanism to stabilize the neuronal environment and confers upon the central nervous system a considerable degree of biochemical autonomy." The recent work of Millen and Hess (1958) has suggested that the barrier lies in the ground substance between the capillaries and the neuroglial felt work and that the ground substance is a mucopolysaccharide. Local injury to the surface of the brain, as by a hot needle, ruptures the capillaries and injures the perivascular ground substance, thus allowing vital dyes and other substances to gain access to the intercellular spaces of the brain. Penetration of these substances beyond the area of injury is prevented by the undamaged ground substance in the surrounding uninjured areas. These observations introduce the possibility of a local accumulation in excess of substances having an excitatory or inhibitory effect as the result of an inward leakage from plasma to brain. The opposite possibility must also be allowed for—leakage from brain to plasma.

Recent experiments by Purpura and others (1958) are of interest in this connexion. They first observed that the intravenous injection of γ-amino-butyric acid produces neither any alteration of surface potentials nor any detectable increase in the brain concentration of GABA, thus confirming other evidence showing that GABA does not effectively penetrate the blood-brain barrier. They then proceeded to effect local damage to the cortex and found that under these conditions GABA given systemically caused changes of electrical potential confined to the region of the local barrier breakdown, comparable with those produced by topical application. Of further interest was the observation confirming previous work, that in the neighbourhood of a lesion produced by freezing with ethyl chloride spontaneous paroxysmal activity would develop—in fact a spike focus. Under these conditions the injection intravenously of GABA caused disappearance of the negative spike, the appearance of high voltage positive sharp waves, and at the end of about 12 seconds a normal record. The injection of GABA in large amounts,

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30 mg./K, would abolish paroxysmal activity for several hours. The authors note that the inhibitory effect thus produced is greater and much more prolonged than that following the topical application of GABA in the region of a spike focus.

Clinical Problems

From this brief review it would appear that there is physiological and biochemical support for the existence of inhibitory systems in the brain which have among their functions that of an anti-convulsant, and that a failure in one or other of these systems may suffice to cause epileptic seizures. This hypothesis does not exclude the possibility of primary excitation, such as might result from an excess of excitatory transmitter substance, having the same effect. There is indeed experimental evidence which supports this.

I shall conclude by presenting some facts of clinical observation which in the absence of scientific interpretation invite speculation. The first is the occurrence of seizures resulting from the presence of an extracerebral tumour, for example a meningioma lying upon the motor cortex. To begin with some assumptions, let us suppose that the persistent discharging lesion, in Jackson's sense, is caused by a local disorder of function involving a block in inhibition or enhancement of excitation. This is generally supposed to be the effect of local circulatory disorder. The next assumption often made is that the seizures are an effect of anoxia. This, however, receives little support from experiment or clinical enquiry. The local ischæmic episodes which we commonly observe as the result of arterial narrowing usually take the form not of an epileptic seizure but transient loss of function. Another possibility would be the local accumulation of waste products as the result of venous obstruction. This has been investigated, so far with negative results (Pope, Morris, Jasper, Elliott and Penfield, 1947). A further possibility worth consideration is whether, either as the result of vascular congestion or deformation of the brain, there may be a local breach in the blood-brain barrier, with local accumulation of a substance which enhances excitation or blocks inhibition; or on the other hand leakage from the brain of an inhibitory substance. This, however, is mere speculation, and it has to be admitted that the question how a meningioma causes seizures is unsolved. Even if it were answered there remain others. Why are the seizures only occasional and by what are they occasioned? This is, of course, a question that applies to epileptic seizures in general, and to which the answer may be in part that seizures may be evoked by specific stimulus patterns. If, as has already been suggested, there is under normal conditions a variable and fluctuating control of afferent inflow, the coincidence in time of two factors, specific stimulus and weak inhibition, might be necessary. It seems essential, however, to invoke

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another factor of a more general kind, if only to explain why of two patients having apparently identical tumours one has frequent seizures and the other few or none. Into this field of enquiry I shall not venture.

We sometimes observe cases in which after a "spontaneous" seizure the patient is confident, with good reason, that he will have a period of complete freedom, and a refractory period may also occasionally be observed after evoked seizures. Through the kindness of Mr. Falconer I have had the opportunity of examining a patient under his care in whom the refractory state was of exceptional interest (Falconer and James, 1959). The case is to be published, but I have permission to refer in advance to those observations which are relevant to the problems under consideration. The patient, a very intelligent male aged 18, was subject to spontaneous seizures, which at the time of his admission to hospital would occur three or four times daily. The attacks were brief and not necessarily attended by loss of consciousness but often caused him to fall, and were therefore a cause not only of inconvenience but danger. He had been aware for some time that after a seizure he would be immune for several hours. He had also learned that he could elicit an attack by rubbing the right side of his face with the back of his right hand. This rubbing, if repeated at a certain rate, would, if the attempt were successful, evoke a sensation described as like something caressing the right cheek and temple. This sensation would then continue spontaneously in a rhythmic or pulsating fashion and end in a seizure. He could usually thus precipitate a seizure if he had had no attack in the preceding two hours, but the shorter the time he had been without a seizure the greater was the duration of the rubbing required to provoke one. Observation by Dr. James revealed a remarkably constant inverse relationship between the amount of stimulation required and the length of time since the last attack. The patient, who was leading an active life, had made practical use of his knowledge, and would retire to a convenient place and provoke a seizure in order to prevent such an occurrence in awkward situations. He proved at operation to have an angeiomatous malformation at an appropriate site in the left post-central gyrus.

There appear to be at least two possible modes of interpreting these observations. According to the first, the local accumulation of an excitatory substance led eventually to an excessive discharge. The excitatory substance, being presumed to be a precursor of the excitatory transmitter substance, was exhausted in the course of the discharge and the refractory period corresponded with that required for re-accumulation. The hypothetical excitatory substance might conceivably be a constituent of normal plasma accumulating locally in excess owing to a leak in the blood-brain barrier. An alternative hypothesis would be that the effect of the local lesion was depression of the tonic inhibitory control of afferent impulses. Either chance stimulation of the appropriate area,

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or self-stimulation, initiated a seizure. The excitation then evoked local augmentation of inhibition, which, having caused cessation of the discharge, continued as a tonic inhibitory state with a gradual decay up to the point at which first a large, and then a smaller, volley of afferent impulses would break through, and finally, if no attack were artificially evoked, the normal afferent inflow would provoke an apparently spontaneous attack. If this latter interpretation should be correct we still have to enquire what are the chemical processes underlying this sequence of events, but it would at least be possible to imagine the local lesion to be causing a defect of function, that is to say, a defect of inhibitory function, which would bring it into line with what has been suggested in myoclonic seizures, and is generally a more satisfactory kind of explanation for the clinician and pathologist than that implied by the concept of local irritation.

Conclusion

It has been possible in this lecture to discuss only a few of the recent advances in neurophysiology and biochemistry. It is in the latter field that further discoveries are to be hoped for which will throw a light into the many dark corners which are now open only to speculation. When the transmitter substances in the brain are known, together with their backgrounds of enzyme and substrate, and when the chemical environment of the nerve cell, and its susceptibility to changes in the constituents of the plasma, are better understood the neurologist may feel less bewildered by the problem of epilepsy than he is today. Meanwhile the work of Hughlings Jackson stands as an example for all students of epilepsy not only to record their observations in the greatest detail but to be constantly asking questions about all that has been observed.

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CLINICAL AND ELECTROENCEPHALOGRAPHIC ASPECTS OF EPILEPTOGENIC LESIONS OF THE MEDIAL SURFACE AND SUPERIOR BORDER OF THE CEREBRAL HEMISPHERE

BY

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INTRODUCTION

EPILEPSY arising from the medial surface and superior border of the cerebral hemisphere is comparatively rare but it is of interest because of the problems it presents in diagnosis. The major contribution to our understanding of the fit patterns to be expected has been made by Penfield and his colleagues at Montreal (Penfield and Erickson, 1941; Penfield and Rasmussen, 1950; Penfield and Kristiansen, 1951; Penfield and Welch, 1951; Penfield and Jasper, 1954). Tükel and Jasper (1952) have reviewed the electroencephalographic findings in a series of cases from the same clinic.

MATERIAL

The present report is based on 7 cases seen at the Maudsley Hospital and the Guy's-Maudsley Neurosurgical Unit. All were referred because of epileptic attacks. Their ages varied from 14 to 45, the average age being 25. The age of onset of attacks ranged from 1 to 22 years, the average age of onset being 11 years. All had detailed neuro-radiological studies including lumbar encephalography and cerebral angiography when this investigation was considered indicated. Each case had repeated electroencephalographic examinations—some also had activation records using either 5 per cent metrazol or 0·5 per cent megimide. Since the value of the epileptic aura in providing localization is greater in those patients with small focal lesions than in those with gross tumours, all cases of known tumour have been excluded from consideration. The lesions in 6 of the 7 cases were subsequently verified at operation. In 4 of the 6 cases the pathological lesion found was a scar, in another it was a small aneurysm. In the sixth case histological examination showed a small area of tuberose sclerosis. The remaining case was not

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operated upon, but it is probable that this lesion too was a scar. The approximate localisation of the lesions is shown in fig. 1.

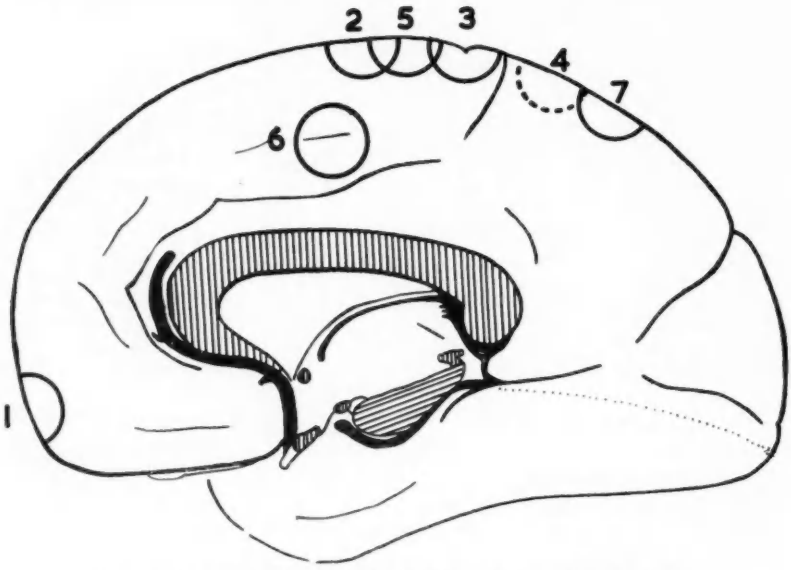

FIG. 1.—This diagram indicates the approximate location of the various lesions.

CASE REPORTS

Case 1.—T. P. M. *Visceral Sensation, Brief Automatism*

A man aged 45 years, who was referred by Dr. Denis Hill to Mr. Murray Falconer, had had attacks since the age of 19. These would begin with a momentary sensation of "pins and needles" rising from his left groin to his epigastrium. He would then lose consciousness and show a brief automatism in which he would be violent and aggressive. The whole attack would last only about one minute. In addition he had been depressed and paranoid for two years, believing his neighbours were talking about him. He had also expressed suicidal ideas on several occasions. On examination he was a man of average intelligence—Wechsler Full Scale I.Q. 110, Verbal Scale 115, Performance Scale 105. He was severely depressed and self-reproachful with ideas of reference. There were no abnormal neurological signs. A radiograph of skull and lumbar encephalogram were within normal limits. Routine electroencephalograms showed a very active spike focus at the right frontal pole. An attack was also induced by intravenous injection of 8 c.c. of 5 per cent metrazol (fig. 2). This led initially to increased activity of the frontal focus but the actual onset of the attack was preceded by a period of 4 seconds during which the firing of the focus was completely suppressed.

At operation Mr. Murray Falconer performed a right frontal lobectomy. Although the brain appeared normal macroscopically, histological examination

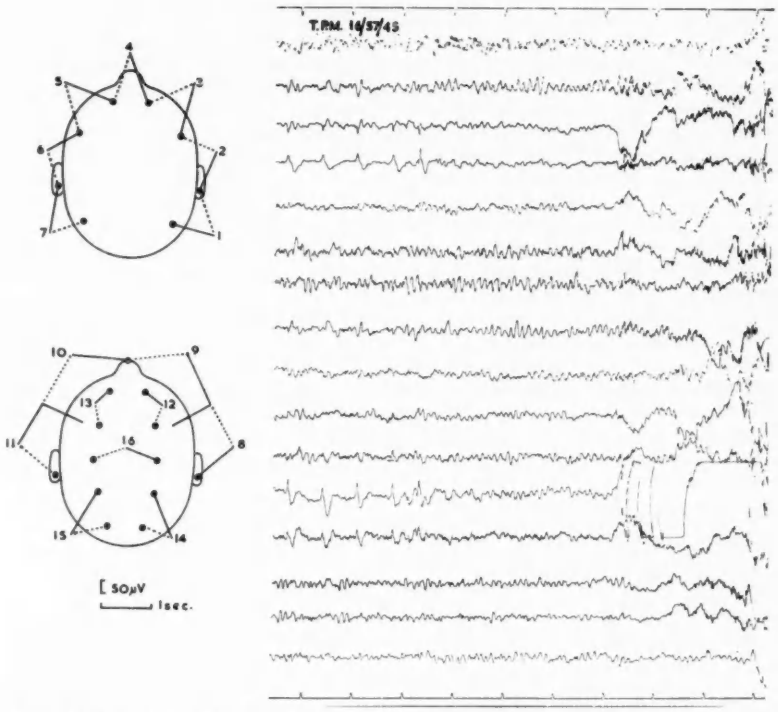

FIG. 2 (*Case* 1).—This record shows the beginning of an attack induced by intravenous injection of 5 per cent metrazol. Note the active spike focus at the right frontal pole and the suppression of spike activity for a brief period immediately preceding the movement artifact.

(Dr. J. B. Cavanagh) revealed a small area at the pole about $2\frac{1}{2}$ cm. in diameter which showed changes characteristic of tuberose sclerosis.

Since operation re-examination has shown no other evidence of tuberose sclerosis. He has had no epileptic attacks but his mental state remains unchanged.

Case 2.—T. L. *Visceral Sensation, Tonic-postural Movement, Speech Arrest*

This was an 18-year-old boy, who was referred by Dr. Denis Hill to Mr. Murray Falconer. He had had attacks for three years. When first seen at the age of 16 years he described feelings in his epigastrium as if his breath was taken away, followed by his right arm and right leg moving out from his body and jerking. There was no change of consciousness. At times he was unable to speak. He also showed a personality change. From being a happy sociable boy he had become irritable and aggressive. He was a voluntary patient in a mental hospital when first seen and remained so for two years until his last admission to the Maudsley Hospital in 1957. There were no abnormal signs on physical examination.

A radiograph of the skull was normal but a lumbar encephalogram showed that the

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whole of the ventricular system was displaced minimally to the right of the midline. There was also possibly minimal medial displacement of the tip of the left temporal horn. A left carotid angiogram added no further information. These changes although minimal were thought to be compatible with a small anterior temporal lobe tumour. At this stage repeated electroencephalograms failed to show an epileptogenic focus. The pneumoencephalographic changes were so slight that craniotomy was not considered justified.

The patient was readmitted in 1957: his behaviour had remained abnormally aggressive and he was suffering approximately 20 fits per day despite very large doses of anticonvulsants. He now described a tingling twitching feeling in the right side of his abdomen and this was accompanied by a stiff feeling in his right leg. In the attack his right arm would abduct to a right angle and flex at the elbow, his left arm would flex and both legs would abduct in an extended position, left more than right. The whole attack was very brief, lasting approximately 30 seconds. The lumbar encephalogram was repeated but showed no change from the previous one. Further electroencephalograms showed a spike focus at the vertex and several attacks were recorded which began with a period of suppression in all areas of both hemispheres (fig. 3). At operation Mr. Murray Falconer found an area of adhesions

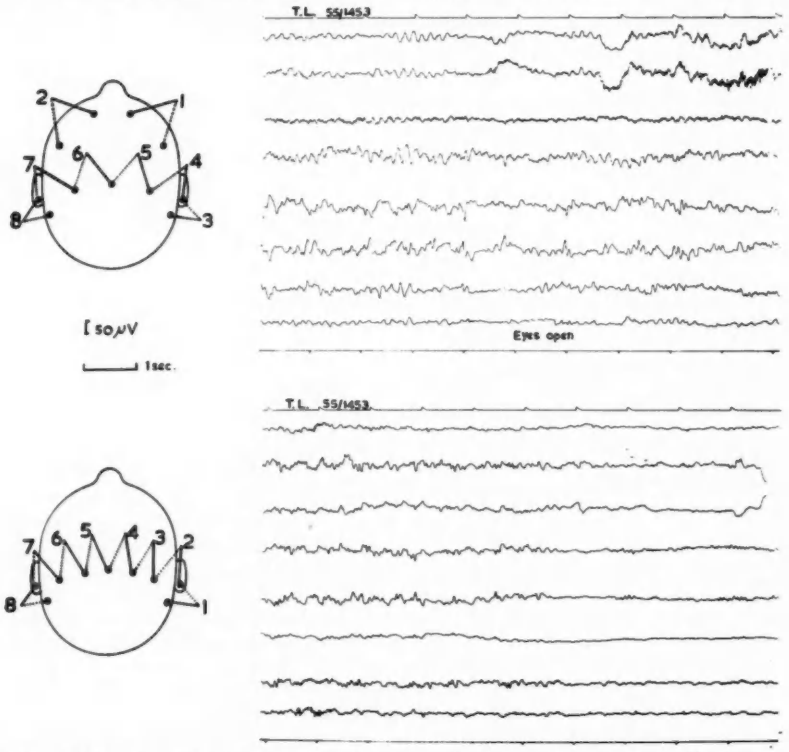

FIG. 3 (*Case* 2).—The upper record shows a spike focus at the vertex. The lower record shows suppression of activity in all areas heralding the onset of an attack.

indicating a meningo-cortical scar about 2–3 cm. long between the superior border of the left frontal lobe and the longitudinal sinus and about the same distance in front of the central fissure. These were excised. Post-operatively his fits have been infrequent although he has had periods lasting one to two days when he has had a series of fits. These periods have been precipitated by emotional disturbance. There has also been some improvement in his mental state. He is still irritable and liable to be aggressive if provoked but on the whole is much more amenable.

Case 3.—P. B. *Visceral Sensation, Genital Sensation and Tonic Postural Movement*

A woman aged 24, who was referred by Dr. Desmond Pond to Mr. Murray Falconer, from the age of 3 frequently had what she called a "shaky right leg." This would last for only a few seconds but would cause her to fall if running. By the age of 10 these attacks began to be precipitated by an unexpected event. Anxiety made her more likely to have them. At the same time the right-sided sensation was accompanied by paræsthesia of the clitoris, which she described as bilateral. Since the age of 15 she had suffered single major fits occurring either following a group of falls or at the end of a series of what she called spasms. These spasms which

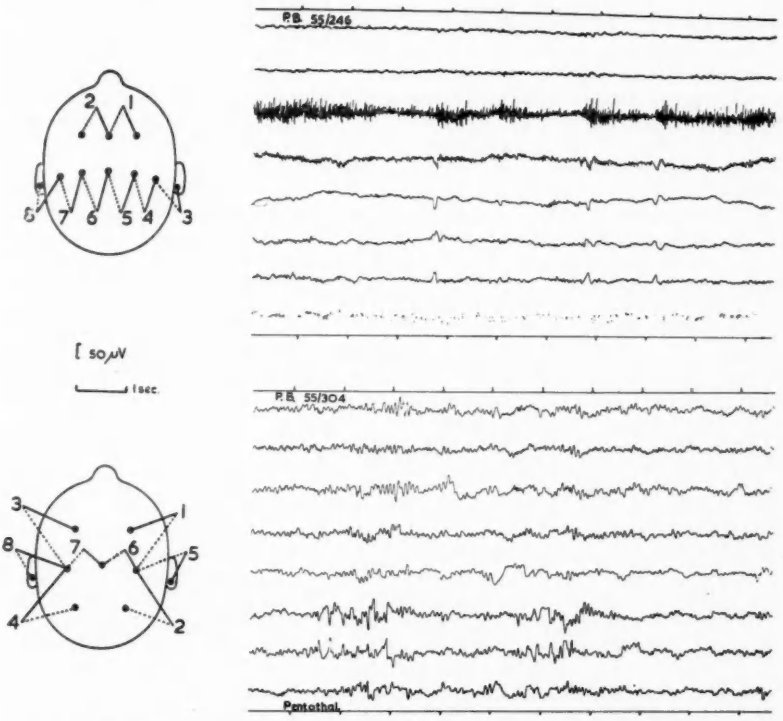

FIG. 4 (*Case* 3).—The upper record shows a focus at the vertex. The lower record shows the same focus under pentothal narcosis.

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occurred every two to three months, were tonic contractions of the right leg and arm—the leg would flex at the knee to an angle of about 140 degrees, the foot would be inverted and the elbow flexed. This tonic contraction lasted about one minute and recurred frequently until terminated by a major fit. After the momentary stiffening she said the leg went limp. At the same time she experienced a turning-over feeling and tingling in the stomach. This sensation occurred in the genitalia as well and she felt as if she was having an orgasm. From the age of 15 this patient had been seen at several hospitals, the diagnosis of hysteria usually being made. She had undoubtedly a grossly hysterical personality with an abnormal sexual history. On examination there were no abnormal neurological signs. A radiograph of skull, lumbar encephalogram and bilateral carotid angiograms were normal. Repeated electroencephalograms showed a spike focus at the vertex (fig. 4). At operation Mr. Murray Falconer excised a tough meningo-cortical cicatrix about 2 cm. by 1 cm. which was found straddling the upper part of the central fissure. Electrical stimulation 2½ cm. deep in the longitudinal fissure reproduced an erotic vaginal sensation. Since operation this patient has had a slight weakness of dorsiflexion of her right foot. There has been no improvement in her fit frequency or personality.

Case 4.—S. H. *Somatic Sensation, Tonic Postural Movement*

A young married woman aged 27 was under the care of Dr. A. Harris. Since the age of 16 she had had frequent attacks of a tonic nature involving the left leg, as well as the other limbs to a lesser extent. In these attacks she would fall slowly to the ground but would not lose consciousness. She had also a very hysterical personality and her attacks were precipitated by emotional disturbances and sudden noises. She claimed she could induce the attacks at will and did so for the doctor's benefit. Having had the attack she would ask "Was that all right?" No sexual aura was obtained from this patient but her husband's attempts at sexual intercourse invariably produced an attack. From the age of 4 she had suffered what she called cramp in her left leg about once a month, when she would call out that her leg was tickling. This got less as time went on. She also admitted that she sometimes got a horrible indescribable feeling in her left foot or a stabbing feeling in her left hip at the beginning of an attack. In the fully developed attack which could also be induced by stroking the dorsum of the left foot, her left arm and leg would extend to the left. This would be followed by extension of her right limbs, then her right arm would flex, followed by flexion of the left knee. If spoken to during an attack she could only reply when it was over.

On examination there were no abnormal neurological signs. A radiograph of the skull was normal. A lumbar encephalogram showed that the third ventricle lay 2 mm. to the right of the mid-line and the whole of the right lateral ventricle including its temporal horn was slightly smaller than the left. Dr. Richard Hoare considered the appearances were consistent with an atrophic lesion of the right hemisphere. The electroencephalogram showed a spike focus at the vertex (fig. 5). An attack was induced, during a recording, by stroking the dorsum of the left foot. Electrically it began with a short burst of low voltage fast activity (20–22 c/sec.). This was followed by a period of bilateral suppression lasting about five seconds. Fast activity at approximately 30–32 c/sec. then appeared with low voltage slow activity. This was succeeded by rhythmic 6–7 c/sec. activity which became slower in frequency and reduced in amplitude. Post-ictally the activity of the focus was very much reduced. This patient was not operated upon but it seems probable that the ætiological factor was a degenerative lesion in the region of the vertex.

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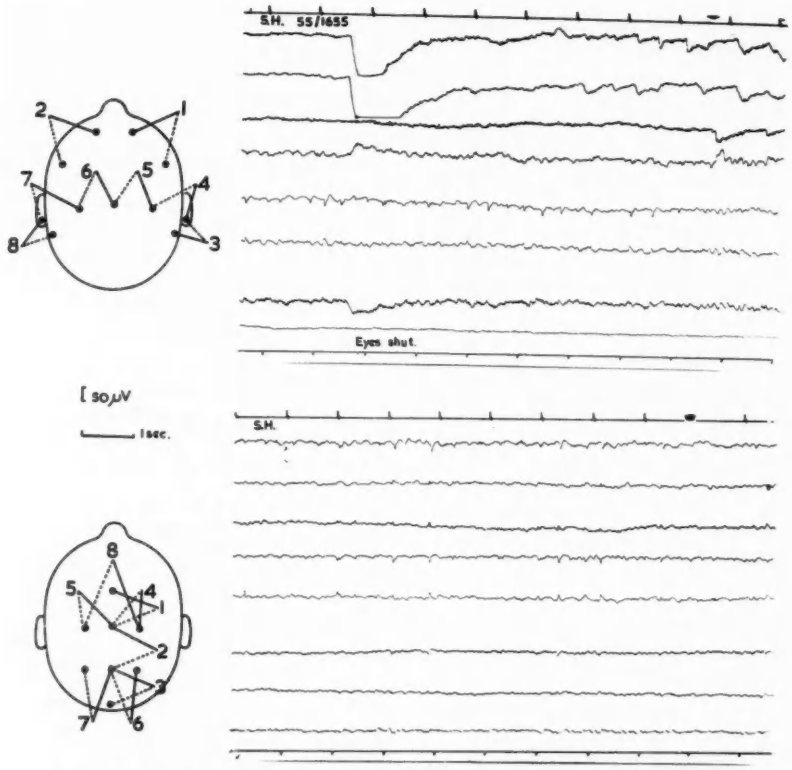

FIG. 5 (*Case* 4).—These records show an active spike focus at the vertex.

Case 5.—R. D. *Jacksonian Motor Movements*

A man of 27 was referred to Mr. Murray Falconer with the history that from the age of 15 he had had focal attacks involving his right leg and arm, sometimes associated with loss of consciousness. The attacks started in the right foot as a feeling of tightness in the region of the ankle. At the same time there was dorsiflexion of the great toe. The tight feeling spread steadily up the leg to the knee and hip, and clonic movements developed. Usually no further spread occurred but occasionally the tight sensation and clonic movements would spread to his right shoulder and upper limb and his head would turn to the left. The patient was aware of his head turning to the left but said he was unable to prevent it. Apart from the tight feeling the only other abnormal sensation experienced was the feeling that his fingers had fallen off. The attacks could occasionally be provoked by rubbing his right foot and at times they could be inhibited from spreading by gripping his right leg with his hand. Once the upper limb was involved consciousness was always lost. In addition he had had at least six episodes in which he said he would wake up to find himself "somewhere he shouldn't be." The last of these episodes had an unfortunate ending. By profession he was a burglar, having a long history of delinquent behaviour and at

least six prison sentences. He was serving a four-year term when he was first seen. The circumstances of his last arrest were as follows. He remembered leaving his home one night to go for a walk as he was feeling slightly "muzzy" after a few drinks although he was not really drunk. The next thing he remembered was being told by the police that he had been found with an amount of stolen money and unopened bottles of whisky in the garden of a house which had been burgled. At first he thought that he had been "framed" but he soon realized that he probably had been responsible. However, he insisted that he must have had some sort of attack as he would never consciously go out to do a job in his ordinary clothes and without gloves, soft shoes and other housebreaking equipment, and then wait around, only running when the police arrived. These shortcomings he felt were an insult to his professional ability. On examination the patient had a right hemiparesis which was more marked in the leg than the arm. The reflexes were also increased on the right side and the right plantar response was extensor. The right leg was also shorter than the left.

A radiograph of the skull was normal. A lumbar encephalogram showed a slight focal dilatation of the anterior half of the left ventricle. The electroencephalogram showed a focus of low voltage 6 c/sec. activity at the mid-line in the frontal region. An attack involving the right leg and arm without loss of consciousness was evoked by metrazol. Electrically this was associated with suppression of activity over the left hemisphere; rhythmic spikes and slow waves being seen over the right hemisphere. At operation a meningo-cerebral cicatrix about 2 cm. in diameter was found on the superior margin of the left hemisphere at the posterior part of the superior frontal convolution. This cicatrix was removed. Two other small scars less than 1 cm. in diameter but not adherent to the dura were also found. One was situated in the inferior frontal convolution and the other was in the superior margin of the hemisphere anterior to the excised scar. Both these scars were left.

Since operation in 1953 this patient had had no further attacks, and has followed legitimate occupations.

Case 6.—L. T. *Somatic Motor Movement*

This woman of 23 was referred by Dr. M. J. McArdle to Mr. Murray Falconer because of two epileptic attacks in the previous six months. Each attack had begun with shaking of her left hand. The patient had tried to control this by holding it with her right hand but she was unable to do so, her left hand was drawn up to her shoulder and she lost consciousness. Four years previously she had an unexplained episode in which she suddenly lost consciousness getting off a train. She had an amnesia for the subsequent twelve hours. Since that time she had intermittent frontal headaches. Two years later she was admitted to another hospital with a subarachnoid hæmorrhage which was verified by lumbar puncture. She had an amnesia on that occasion for five days and on regaining consciousness had a left hemiparesis. On examination the left hemiparesis was still present being more marked in the upper limb. The left tendon reflexes were slightly brisker than the right but both plantar responses were flexor. There was no detectable sensory loss. A right carotid angiogram showed a small aneurysm or angioma lying on the supra-callosal branch of the right anterior cerebral artery just behind the coronal suture. The electroencephalogram showed a spike focus to the right of the mid-line at the vertex. At operation, Mr. Murray Falconer excised a spherical aneurysm about 1 cm. in diameter at the point of branching of the right anterior cerebral artery. It was firmly adherent to the falx by fibrous tissue. A small cystic cavity with hæmosiderin-stained walls was found in the mesial portion of the frontal lobe in association with the aneurysm.

Since operation the patient has continued to have infrequent attacks.

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Case 7.—C. B. *Somatic sensation*

A boy of 14, who was referred by Dr. Denis Hill to Mr. Murray Falconer, had suffered from frequent daily attacks since the age of 18 months. Since the age of 5 these consisted of a feeling of numbness and cramp starting in the right calf and spreading up the leg before subsiding. These attacks would last about one minute, and afterwards the leg would be weak for periods of half an hour or even longer. Less frequently, from the age of 11, the same aura proceeded within 10–15 seconds to loss of consciousness and a generalized convulsion. The probable ætiological factor in this case was birth trauma. He had had a forceps delivery and was said to have had severe marking of the scalp. On examination there were no abnormal neurological signs except that the right knee-jerk was brisker than the left. The radiograph of skull was normal. A lumbar encephalogram showed a focal dilatation in the posterior part of the left lateral ventricle. An electroencephalogram showed a spike focus at the mid-line in the parietal region. At operation, carried out by Mr. Murray Falconer, a small scar $2\frac{1}{2} \times 2 \times 1\frac{1}{2}$ cm. was seen immediately behind the central fissure on the superior border of the parietal lobe. Stimulation here reproduced the aura. The scar was excised.

Since operation this patient has had only very infrequent sensations of tightness in the calf. These last only 10–15 seconds, are not followed by weakness of the leg, and cause no incapacity.

Clinical Findings

The type of initial epileptic pattern found in this series is shown in the following table.

Type of Aura	*No.*
Visceral sensation	1
Visceral sensation and somatic motor movement	2
Somatic motor movement	2
Somatic sensation and somatic motor movement	1
Somatic sensation	1

It will be seen that three patients experienced a visceral sensation at some stage of the attack. These were Cases 1, 2 and 3. In Case 1 a sensation of pins and needles in the left side of the abdomen was followed by a brief automatism. In this case the lesion was at the right frontal pole. In Case 2 in which a tingling sensation of the right side of the abdomen was associated with a tonic postural movement and speech arrest the lesion was in the supplementary motor area. In Case 3 an epigastric sensation was accompanied by a genital sensation and a tonic postural movement. In this case the lesion was a scar at the upper end of the central fissure. In addition to Cases 2 and 3 a tonic postural movement also occurred in Case 4. This was preceded by a sensation in the leg. The lesion in this case was not known but the epileptic pattern indicates that the cortical discharge occurred first in the postcentral sensory cortex and then spread forwards to involve the supplementary motor area. Two of the remaining cases (Cases 5 and 6) showed epileptic patterns implicating the motor cortex. In these cases the lesions, one an aneurysm and the other a scar, were

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situated in the posterior part of the motor cortex. In the remaining case with sensory attacks involving the lower limb the lesion was a scar in the upper border of the parietal lobe.

Electroencephalographic Findings

Spike foci were found in 6 of the 7 cases. In each instance the focus consisted of single spikes. The remaining case showed a focus of 6 c/sec. activity. There was no example of subcortical epileptic activity. Attacks were recorded in 4 out of the 7 cases. In 2 of these 4 cases, the attacks were evoked by metrazol or megimide. In a third case a spontaneous attack was recorded as well as both metrazol and megimide-induced attacks. In the last case an attack was induced by stroking the dorsum of the foot. In each attack the onset was characterized by suppression of electrical activity.

It must be emphasized that once the site of the lesion is suspected to be in the parasagittal areas repeated electroencephalograms including pentothal, metrazol and megimide activation studies may be necessary to determine the focus. For accurate localization transverse and sagittal lines of electrodes often closely spaced may be needed.

Discussion

Clinical.—A number of fit-patterns are associated with epileptogenic lesions involving the medial surface of the hemisphere. Prominent among them are those arising in, or involving spread into, the supplementary motor area. The clinical associations of epilepsy in this region were first described by Penfield and Welch (1951) and confirmed by Erickson and Woolsey (1951). According to Penfield and Welch the area lies almost entirely on the medial aspect of the hemisphere just in front of the Rolandic leg area and above the cingulate sulcus. Epileptic activity arising spontaneously from, or electrical stimulation of, this area is said to produce movements quite distinct from those produced in the motor cortex. They are often complex and have been likened to the assumption of a posture, frequently one in which the contralateral arm is abducted and externally rotated at the shoulder and flexed at the elbow with the head turned towards the arm. In addition the extremities of both sides as well as the trunk are often involved in the posture. Occasionally there may be rhythmic movements of either an ipsilateral or contralateral limb. Stimulation, or spontaneous epileptic activity, may also produce vocalization (Penfield and Welch, 1951; Sweet, 1951) and slowing or arrest of voluntary movement or speech. Sensory experiences have also been noted. These are usually related to the autonomic system, e.g. an abdominal sensation. A further example of this is a case with a right frontal oligodendroglioma.

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A highly intelligent 34-year-old man, under the care of Mr. Murray Falconer, had a two-year history of attacks characterized by an aura of abdominal and bladder sensation followed by a momentary inaccessibility with subsequent confusion often associated with incontinence. He said that he sometimes had a feeling that he was full of wind and had a desire to micturate. Having passed wind and urine he would feel much better. On examination the only abnormal neurological finding was a right extensor plantar response. A radiograph of the skull showed a calcified shadow in the right frontal region. An electroencephalogram showed a sharp-wave focus to the right of the mid-line in the superior frontal region more or less accurately reflecting where the tumour was seen to approach the surface of the brain at operation. In this case an attack was recorded which was confined to the right hemisphere.

If the initial aura phenomena include visceral sensations, speech arrest or tonic postural movements, confusion sometimes occurs. This is well illustrated by Case 2. It will be seen that at first this patient was thought to be suffering from temporal lobe epilepsy. Indeed surgical exploration of the temporal lobe was considered at one stage. The factors in favour of this diagnosis were the abdominal sensation, inability to speak and the aggressive personality disturbance. It might be thought that the sensation in the abdomen which was experienced in this case or indeed in Case 1 is unlike that found in temporal lobe epilepsy—in the latter it is unusual to find it lateralized to one side but in Penfield's material the common temporal lobe aura—the sensation beginning in the epigastrium and rising to the throat is also often met with in lesions anterior to the pre-central sulcus although he does not seem to have met it as far forward as the frontal pole.

Until Penfield's work on the supplementary motor area, inability to speak at the beginning of an attack was usually considered to indicate involvement of the dominant temporal lobe. It is interesting that Hughlings Jackson (1882) described a patient with attacks beginning in the right foot consisting of tonic-clonic movements of the right limbs and to a lesser degree the left limb, usually without loss of consciousness. Inability to speak was a prominent feature in the attacks. On one occasion the patient was unable to speak for three and a half minutes. No spasm was observed but the patient complained of a "twittering feeling" in his right great toe. At post-mortem a glioma was found in the posterior part of the superior frontal convolution.

Tonic postural movements with no disturbance of consciousness may also give rise to errors of diagnosis. No mistake is likely to be made if the common postural movement occurs, i.e. raising of the contralateral arm and the turning of the head towards the arm. However, if the tonic spasms involve mainly the lower limb as in Cases 3 and 4 the epileptic nature may be overlooked. Both these cases had previously been diagnosed as hysterical. Both patients had hysterical personalities. Case 4 obviously took delight in reproducing her attacks. The attacks in both Cases 3 and 4, which were very brief, were precipitated by anxiety

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and startle. It is of note that Gastaut (1954) mentions only 2 cases of startle epilepsy. Clinically they suffered tonic seizures of the lower limb and both had lesions in the supplementary motor area.

With lesions anterior to the supplementary motor area Penfield and Kristiansen (1951) pointed out that although epileptic attacks originating in front of the pre-central sulcus usually commence with the turning of the head and eyes to the opposite side, rarely to the same side, the farther forward the attacks originate the more likely are they to begin with loss of consciousness. They do not appear to have met with visceral sensation as far forward as the frontal pole as in Case 1. On the other hand Tükel and Jasper (1952) indicate that possibly mental confusion occurs in some cases before the onset of unconsciousness and that short-lasting stereotyped automatisms may occur instead of generalized convulsions. Case 5 illustrates the point that post-ictal automatisms of considerable duration may occur with epileptogenic lesions outside the temporal lobe. Hill in a review of psychomotor seizures in 1949 pointed out that at least one-third arose outside the temporal lobe. Nevertheless it is probable that this figure is an over-estimate as at that time sleep records with or without basal electrodes were rarely used.

Epileptic attacks beginning immediately behind the supplementary motor area give rise to clonic movements or sensations of the contra-lateral lower extremity and are usually easily recognized. Penfield states (Penfield and Jasper, 1954) that in at least 50 per cent of these cases ankle movement is elicited by electrical stimulation within the longitudinal fissure and sometimes even knee and hip movements. Scarff (1940) on the other hand denies that there is any representation of the lower limb on the lateral convexity.

The precise area of cortical representation of the genitalia is in doubt. Penfield (Penfield and Jasper, 1954) could find no motor representation and it is not altogether clear whether the sensory representation is posterior to or below the foot sensory area. In his experience the sensation produced by electrical stimulation never had any erotic quality and unlike Case 3 was always in the contralateral half of the genitalia. Erickson (1945) described a remarkable case of a woman who for sixteen years from the age of 43 had suffered attacks of feeling "hot all over" as if she were having coitus associated with marked increase of libido. She was twice an in-patient with a diagnosis of nymphomania until finally an angioma was removed from the upper end of the right Rolandic sulcus on the medial surface of the hemisphere. This patient said that although the feeling was a pleasurable sensation like ordinary intercourse it was limited to the opposite side of the vagina. Closely related to the cortical representation of the genitalia is that of rectal sensation. Scarff (1940) was the first to report producing focal contractions of the rectal sphincter in man by the electrical stimulation of a point midway between

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the superior border of the hemisphere and the corpus callosum. A clinical example of this has been encountered.

A 43-year-old woman was referred to Mr. Peter Schurr with a three-month history of depression and loss of interest. She complained that for ten weeks she had had recurrent transient sensations of contraction and dilatation of the anus. This feeling was immediately followed by a transient but definite weakness of her left hand and the whole of her left lower limb which suddenly would feel normal again after a few seconds. These two separate and distinct phenomena occurred every day lasting for the same period but increasing in frequency up to ten times daily until about two weeks prior to admission when they stopped. During these attacks she never lost anal control. On examination there was bilateral papillœdema. Reflexes were normal except that both plantar responses were extensor. There was also minimal sensory loss in the left hand and foot. A right carotid angiogram showed a pathological circulation in the right posterior frontal region high up in the hemisphere and deep to the medial surface. Operation confirmed the location of the tumour which proved to be an astrocytoma grade IV.

Penfield (Penfield and Jasper, 1954) has reported that in the mesial parietal region just posterior to the postcentral leg area there is some evidence for a supplementary sensory area. Stimulation of this area, in his experience, produced sensations in the extremities of both sides similar to those produced in the Rolandic area, i.e. somatic sensation as opposed to visceral sensation produced by stimulation of the supplementary motor area. In the occipital cortex epileptic attacks began with visual sensation and often turning of the head and eyes to the opposite side. There is no example in this series of an epileptogenic lesion in either the supplementary sensory area or occipital cortex.

Electroencephalography. — The electroencephalogram provides confirmation of the localization and may be vital when surgery is being considered. Electroencephalographic localization of lesions in these areas has always been recognized as difficult. First, a focus here is liable to be further removed from the nearest possible electrode placed on the intact skull than a similar focus on the convexity of the hemisphere. Secondly, it has long been suggested (Penfield and Jasper, 1946; Jasper, 1951) that lesions of the medial surface are particularly prone to give rise to bilaterally synchronous discharges and are thus apt to be dismissed as cases of *petit mal*. It is believed that the cortical focus fires the subcortical structures responsible for bilateral synchronous discharges. In 1952 Tükel and Jasper reviewed the electroencephalographic findings in a number of verified parasagittal epileptogenic lesions, including birth injury, head injury, brain tumours and cortical atrophy. The most striking feature of the electroencephalograms in 26 of 31 cases was the occurrence of bilaterally synchronous spike and wave complexes ("secondary bilateral synchrony"). Although these bursts resembled those seen in primary bilateral synchrony (*petit mal*) Tükel and Jasper considered that there were certain atypical features

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that enabled them to be differentiated. Among the distinguishing points were the following:

(1) The frequency usually varied between 2–3½ c/sec. although occasionally it was even faster. It was most commonly at 2–2½ c/sec.

(2) The form and relationship of the spike to the wave component was less regular.

(3) Isolated focal discharges from one hemisphere might be seen preceding a bilaterally synchronous burst.

(4) Consistent asymmetry of the complexes was often seen over homologous areas of the hemispheres. In addition a phase reversal in an equipotential area might be seen to one side of the mid-line.

No case in this series conforms with these findings. Indeed no subcortical-type discharges were seen in these 7 cases. Tükel and Jasper suggested as a possible explanation that some of their patients who showed this finding had rather extensive areas of atrophy and in these cases both cortical and subcortical areas may have been involved in the pathological processes. This is a convincing theory. It would also help to explain the conflicting findings in the present series in which all the lesions were small and discrete. However in some of the cases of Tükel and Jasper circumscribed lesions were reported and these showed subcortical-type epileptic activity in the EEG. Whatever the explanation, it seems probable that secondary bilateral synchrony resulting from lesions in these areas is less frequent than Tükel and Jasper suggest. Finally they suggested that suppression of activity either preceding or during an epileptic attack, although common in temporal lobe seizures was only seen in the supplementary motor area of their parasagittal cases. The attacks recorded during the investigations of Cases 1, 2 and 4 show that suppression of activity may occur not only with attacks beginning in the supplementary motor area but also with those beginning at the frontal pole.

Summary

(1) The clinical and electroencephalographic findings have been reported in 7 cases with small discrete lesions of the medial surface or superior border of the hemisphere. 6 were verified at operation.

(2) The aura phenomena that suggest localization in these areas were discussed. These included visceral, genital and anal sensation, tonic postural movements, and sensory motor phenomena involving the lower limb.

(3) The electroencephalogram in the majority of cases showed a spike focus. There was no example of secondary bilateral synchrony.

I wish to thank Mr. Murray Falconer, Dr. A. Harris, Dr. M. J. F. McArdle, Dr. D. A. Pond and Mr. Peter Schurr for permission to report

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POST-EPILEPTIC PARALYSIS

A Clinical and Experimental Study[1]

BY

JOHN S. MEYER AND H. D. PORTNOY

THE nature of the transient paralysis which occasionally follows an epileptic seizure is a subject which has interested neurologists for over a century. The purpose of the present paper is to review the subject in the light of new clinical and experimental observations which permit a better understanding not only of post-epileptic hemiplegia (Todd's paralysis) but also of other states of impaired cerebral function which commonly follow epileptic seizures such as stupor and confusion.

The first clear description of post-epileptic paralysis was made in 1855 by Todd. He defined "epileptic hemiplegia" as follows: "a patient has a fit, distinctly of the epileptic kind; he comes out of it paralysed in one side of the body; generally that side is paralysed which had alone been convulsed, but the paralysis may occur where both sides had been convulsed equally. The paralytic state remains for a longer or shorter time, varying perhaps from a few minutes or a few hours to three or four days or even much longer. It then goes off, improves, until the next epileptic fit, when a train of phenomena, precisely the same recurs with like result." Todd reported numerous cases noting in many that immediately after the seizure the paralysed limbs were flaccid ("relaxed muscles"). In at least two of the cases he described the paralysis preceded the seizure and it is possible that such cases were suffering from occlusive disease of the internal carotid artery. Todd himself rejected "cerebral congestion" or "compression" as the "paralysing cause" and attributed the paralysis to cerebral exhaustion. He men-

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tioned that the after-effects of a seizure might vary from stupor or mental confusion to motor paralysis depending on the site of discharge. After examination of the brain in 2 of his patients who died he concluded that "this state of exhaustion is very apt to continue as one of weakened nutrition, in which the brain tissue is more or less in the condition of white softening."

Robertson (1869) confirmed Todd's observations and reported 4 similar cases of his own with a gross description of the brain at necropsy in one of them who suffered from post-traumatic epilepsy complicated by osteomyelitis of the skull. He shared Todd's view that paralysis following epileptic seizures was due to exhaustion of those portions of the brain most involved by the discharge.

Jackson (1875, 1876, 1881) extended the clinical observations of Todd and Robertson and emphasized the difference between paralysis *following* a seizure and loss of function *during* a seizure and proposed the more satisfactory term "post-epileptic paralysis." He described cases of post-epileptic aphasia, mania, stupor, sensory loss and motor paralysis and classified all these states as "temporary, functional, exhaustion paralysis of nerve fibres" without any necessary structural alteration although he recognized that brain tumour and syphilis were commonly causes of seizures followed by paralysis. He commented on the similarity of post-epileptic hemiplegia to hemiplegia resulting from occlusion of the middle cerebral artery and mentioned his belief that unilateral seizures with hemiplegia depended on disease in the region of the middle cerebral artery. In discussing the nature of temporary post-epileptic paralysis he drew attention to the analogous, flaccid paralysis seen in the frog after experimental convulsions produced by strychnine or electroshock. Jackson argued cogently that the paralysis was not due to respiratory hypoxia during the seizure since it might follow convulsions without respiratory embarrassment. He also noted that recurrent seizures may occur in the paralysed limbs before any functional use is regained, offering the explanation that the epileptic discharge is a far greater stimulus to the exhausted area than attempted volitional movement.

After such detailed clinical description little more was added until the development of new recording techniques. Denny-Brown and Robertson (1934) recorded the cerebrospinal fluid pressure, respiration and myograms in patients with recurrent seizures and epilepsia partialis continua. Their records showed an increase of cerebrospinal fluid pressure during seizures. The authors discussed the periodicity of seizures and post-epileptic paralysis and concluded that these phenomena were related to changes in neuronal threshold.

Penfield and co-workers (1939) and Jasper and Erickson (1941) published clinical and experimental observations of EEG, blood flow

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and pH during epileptic seizures. By the use of thermocouples implanted in cerebral cortex it was shown that there was a localized or generalized increase in cerebral blood flow during seizures but concluded that in spite of the increased blood flow there was "no reason to conclude that the greatly increased neuronal need for oxygen was satisfied during a seizure and that the brain might still be in a state of severe anoxæmia." Excessive neuronal activity commonly resulted in a marked decrease in cortical pH but the onset, intensity, duration and form of the epileptic discharge were not appreciably affected by variation in cortical pH.

Jasper and Erickson noted in contrast to lack of effect of pH on cortical discharge that apnea was followed within 10–30 seconds by complete arrest of electrical activity of the cortex even during violent discharge. It was concluded that adequate oxygen supply was essential for maintenance of epileptiform activity.

In reviewing the subject Penfield and Jasper (1954) expressed the view that "cerebral neurones function in a delicate balance. Their metabolic rate is high, their margin of safety small. Local and general reactions of cerebral blood vessels provide an efficient mechanism for adjusting the supply to the varying needs during activity but the mechanism is inadequate for the excessive firing of the epileptic discharge. A relative ischæmia develops even with maximum reactive hyperemia, the demand is greater than the supply." In addition, they mention that the electrographic pattern of a local cortical discharge is characterized by spike activity followed by a phase of "exhaustion or extinction" in which the EEG is isoelectric and this is followed by a phase of slow waves during recovery.

Stone, Webster and Gurdjian (1945) showed that during convulsions in the dog there is an increase in cerebral lactic acid, a decrease in phosphocreatine and a corresponding increase in inorganic phosphate. Adenosine triphosphate is unchanged. The changes during convulsive activity were the same as those occurring during respiratory anoxia but in their experiments this possibility was excluded by the use of a mechanical respirator.

By the use of the polarograph electrode Davies and Remond (1946) measured the oxygen tension and oxygen consumption of the cerebral cortex during metrazol convulsions. Immediately following the EEG signs of seizure activity there was a decrease in oxygen tension of cortical venules and tissue space but not of the pial arterioles which maintained a constant oxygen tension. Their experiments showed that cortical oxygen consumption is increased during seizures, but no measurements were made of cortical oxygen tension in the post-ictal state nor was any study made of any relationship that might exist between changes in cortical oxygen tension and the periodicity of the epileptiform discharge alternating with depressed cortical activity.

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Ralston's recent investigation (1958) of the electrographic properties of ictal and interictal discharges has failed to reveal any different explanation for the cessation of the seizure discharge than that proposed by Moruzzi (1950) who concluded that the duration of the interval between successive discharges must depend upon a phase of neuronal exhaustion.

Successful experiments designed to demonstrate the exact nature of post-epileptic "exhaustion" have not yet been published as far as we can determine. During the course of an earlier investigation on factors producing transient hemiparesis in the monkey following occlusion of the middle cerebral artery it was noted that spontaneous seizures in these animals resulted in transient hemiplegia (Meyer, 1959*a*). During the stage of hemiplegia the cortical oxygen tension was low in the ischæmic territory and when the oxygen tension was restored recovery from hemiplegia followed. Such chance observations prompted the present series of clinical and experimental observations. In the clinical studies to be reported here electroencephalographic, angiographic and clinical observations were made on nine patients suffering from recurrent seizures associated with post-epileptic paralysis. In addition, experimental studies were performed in which localized and generalized seizures were induced in monkeys and cats after occlusion of one middle cerebral artery. Observations were made to note any functional deficit following the seizures and to correlate any relationship that might exist between cortical oxygen tension and the periods of epileptiform discharge alternating with depressed cortical activity. Measurements of cortical stimulation threshold were made before and during the stage of post-epileptic paralysis together with observations of any influence that repeated seizures of various duration might have on the course of recovery from resulting paralysis.

Clinical Observations

9 patients with seizures followed by various types of post-epileptic paralysis have been studied in detail. For the sake of brevity the case material is presented in summary in Table I and two illustrative cases have been selected for more complete presentation at the end of this section. Of the 9 patients, 3 suffered from Jacksonian seizures followed by transient hemiplegia, 3 from epilepsia partialis continua followed by transient paralysis of the affected limbs and 3 from post-epileptic confusion or stupor. 3 suffered from status epilepticus. One of the last group, Case 9, had focal temporal lobe seizures caused by tumour invading the left temporal lobe.[1] In 5 cases, it was possible to make

[1]EEG records of Case 9, made during a temporal lobe seizure with automatism, followed by post-ictal confusion have not been illustrated here but have been published elsewhere with a detailed case history (Meyer, 1959*b*).

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TABLE I

Case	Age in years	Diagnosis	Type of seizure	Post-epileptic phenomena	Carotid arteriogram	EEG
1	45	(1) Thrombosis left middle cerebral artery (2) Hypertension (3) Diabetes	Epilepsia partialis continua, right arm and leg	Flaccid right hemiplegia 24 hours	Occlusion branches of left middle cerebral artery	Localized spikes in left central region followed by slow waves
2	62	(1) Atherosclerosis of left internal carotid artery (2) Hypertensive cardiovascular disease	Jacksonian seizures right arm and leg	Right hemianopia, hemiparesis and rigidity 3 hours	Atherosclerosis left internal carotid artery	Localized spikes in left central region, followed by slow waves
3	58	(1) Generalized atherosclerosis (2) Atherosclerosis and stenosis of left internal carotid artery	Jacksonian seizures right arm and leg	Flaccid monoparesis and sensory loss right arm 1 hour	Stenosis and atherosclerosis left internal carotid artery	Spikes in left central, parietal and occipital region, slow waves
4	32	Post-traumatic epilepsy	Status epilepticus with right sided Jacksonian convulsions	Flaccid right hemiplegia, hemianopia and hemisensory loss 4 hours	Normal	Generalized paroxysmal dysrhythmia with left temporal preponderance including slow waves
5	68	(1) Generalized atherosclerosis with gangrene left leg (2) Occlusion of right middle cerebral artery (old)	Generalized seizures and epilepsia partialis continua left arm and leg	Left hemianopia, flaccid left hemiplegia 4 hours	Not performed	Generalized dysrhythmia with right sided spikes. Low voltage slow waves during paralysis
6	79	(1) Generalized atherosclerosis (2) Thrombosis of both middle cerebral arteries	Epilepsi partialis continua left arm and leg	Flaccid left hemiparesis 12 hours	Not performed	Right centro-temporal spikes followed by right sided delta waves during paralysis
7	3/12	Idiopathic epilepsy	Generalized status epilepticus	Stupor or coma 5 days	Not performed	Generalized spike activity followed by diffuse electrical quiescence and slow waves in recovery phase
8	5	Idiopathic epilepsy	Status epilepticus, staring, levitation left arm, stupor	Stupor and confusion 24 hours	Not performed	Bilateral spikes with left centro-temporal preponderance of slow waves in confusional state
9	8	Astrocytoma left temporal lobe	Automatism	Stupor and confusional state 3 hours	Not performed	Left temporal spike focus followed by diffuse spikes and left temporal delta focus in post-ictal state

left temporal delta focus in post-ictal state

continuous EEG records during the seizure and post-epileptic state. In one case 16 mm. motion pictures were made during post-ictal hemiplegia and recovery for purposes of comparison with the experimental observations that will be described in a later section.

In 4 cases with severe post-epileptic hemiplegia percutaneous carotid arteriograms were performed by Dr. Sheila Sheehan. In Case 4, the internal carotid system appeared to be entirely normal (a 32-year-old male with post-traumatic status epilepticus). In the remaining 3 the arteriograms were considered to be abnormal (Cases 1, 2 and 3). One disclosed consistent failure of the dye to fill the ascending branches of the middle cerebral artery on the affected side (interpreted as consistent with occlusion of these vessels) and the remaining 2 showed stenosis and tortuosity of the internal carotid artery on the affected side.

Illustrative Cases

Case 1.—Detroit Receiving Hospital No. 246826. Progressive thrombosis of right middle cerebral artery, epilepsia partialis continua followed by transient hemiparesis and eventual permanent hemiplegia. Hypertensive cardiovascular disease and diabetes mellitus.

This 45-year-old negro male was admitted to the neurological ward of the Detroit Receiving Hospital on June 4, 1958, complaining of numbness and jerking of the right hand for two days. Otherwise his health had been good and there had not been earlier neurological symptoms. The movements of the right hand were rhythmical occurring twice a second and consisted of rapid flexion movements of fingers, thumb, hand and forearm with sparing of the shoulder. After examination, 100 mg. of diphenylhydantion (dilantin) were administered intravenously and the dose was maintained by oral capsules three times daily thereafter. A few minutes after the injection the seizure ceased and he was noted to have flaccid paralysis of the right arm and hand and a central type of paresis of the right face. Movement at the shoulder was not impaired but the hand was totally paralysed and little movement was possible at the elbow.

Mental examination and speech were normal. There was no papillœdema and no abnormality of the other cranial nerves. The tendon-jerks were absent in the right arm but were active in the left arm and symmetrical in the lower extremities, the plantar reflex on the right was extensor while that on the left was flexor. Pin-prick and touch sensation were diminished in the right hand to the wrist with absence of position sense in the fingers and astereognosis of the right hand.

General examination revealed narrowed retinal arterioles with nicking of the veins at the points of crossing. The blood pressure was 190/118, the pulse was regular at 100 per minute and body temperature was normal. The heart was enlarged beyond the midclavicular line on the left at the fifth thoracic interspace. There were harsh systolic murmurs over the apex and in the aortic area. The abdominal organs were not enlarged and the arterial pulses in the neck and extremities were readily palpable.

Twelve hours after the seizure had ceased the sensory examination was normal and the strength was improved in the right elbow, hand and fingers. The tendon-jerks were now symmetrical. Twenty-four hours later strength of grip in the right hand measured with a dynamometer was half that on the left but the next day the strength was approximately equal on both sides.

Lumbar puncture yielded clear cerebrospinal fluid with an initial pressure equivalent to 160 mm. of water and a final pressure equivalent to 60 mm. of water. There were

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no cells present, total protein was 42 mg. per cent and determinations of chloride and sugar content were within normal limits. The Kline test was negative.

Electroencephalogram showed a background rhythm of well modulated alpha with occasional short bursts of spikes followed by slow waves which were localized to the left central region and appeared to have deep origin.

Total blood lipids were 890 mg. per cent and total cholesterol was 286 mg. per cent (high normal values). Urine analysis was normal. Fasting blood sugar was 120 mg. per cent but a glucose tolerance curve was compatible with latent diabetes (remaining between 200 and 250 mg. per cent for five hours). Blood sickle-cell preparation was negative.

Left carotid arteriogram showed widening and tortuosity of the internal carotid artery with consistent failure of filling of the ascending frontal branches of the middle cerebral artery although both anterior cerebral arteries were well filled. There was no displacement of the anterior or middle cerebral vessels.

He improved steadily until the seventh day when he developed a right hemiplegia and aphasia during an episode of hypotension with a fall of blood pressure to 140/90. In spite of intravenous noradrenaline and heparin and oral dicoumarol there was no striking improvement. He slowly regained use of his right leg and some return of speech but at the time of discharge to a convalescent home there was spastic paralysis of the right arm and residual motor dysphasia. It was concluded that there had been further thrombosis of the left middle cerebral artery.

Case 2.—Detroit Receiving Hospital No. 232654. Hypertensive cardiovascular disease with cerebral arteriosclerosis, atherosclerosis of left internal carotid artery and atherosclerotic aneurysm of the innominate artery.

The patient was a 62-year-old negro woman who had been treated at the Detroit Receiving Hospital for the past twenty years for essential hypertension. She was admitted to the neurological service because of Jacksonian seizures. The seizures began with clonic jerks of the right hand, spreading in the next few minutes to the right shoulder and leg with some twitching of the face but without loss of consciousness. She also reported the sensation of flashing lights in the right visual field which were described as "black and white without any colour component." There were no paræsthesias. One hour after onset the seizure subsided spontaneously, and upon examination at this time she was disorientated to time, place and person and was unable to give an account of why she had been admitted to hospital. She understood simple commands and obeyed them. There was a central type of right facial paralysis and her speech was thick. Arcus senilis was present bilaterally and the fundi showed thickened arteriolar walls with numerous old brown hæmorrhages and white exudates. A right hemianopia was present together with a palsy of gaze to the right. Tone was increased in the right arm and leg with slight hemiparesis. The reflexes were increased on the right and the right plantar reflex was extensor.

The body temperature was 98° F., the blood pressure was 180/140, the pulse was regular at 100 per minute and respirations were 20 per minute. Examination of the chest revealed no abnormality other than enlargement of the heart to the anterior axillary line and a soft systolic murmur at the apex.

Her paresis and hemianopia persisted for three hours after which time the only neurological deficit was an inability to name some objects placed in her right visual field, but this defect was not present twenty-four hours later.

Records of a previous admission showed that she had been admitted seven months earlier with signs of hypertensive encephalopathy. During convalescence she had suffered from two episodes of right-sided Jacksonian seizures followed by post-epileptic hemiplegia, and had been examined and treated by us at that time. Therapy

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had consisted of reserpine and apresoline with reduction of her blood pressure from 240/120 to 180/90, resulting in improvement in her neurological status. On the second admission the same treatment was again instituted to prevent a rise in her blood pressure and in addition, 100 mg. of dilantin was prescribed three times daily.

Electrocardigram was interpreted as normal. Hæmoglobin and white blood cell count were within normal limits. Urine analysis showed a fixed specific gravity between 1007 and 1012, 3 plus albumin and a few white cells and granular casts. Total blood lipids varies between 1,027 and 1,346 mg. per cent on four determinations and total cholesterol varied between 399 and 400 mg. per cent (these values are abnormally high). Blood urea nitrogen was 16 mg. per cent. Blood sugar was 85 mg. per cent and determinations of plasma carbon dioxide, calcium, phosphorus, sodium and potassium were normal. Chest roentgenograms showed generalized enlargement of the heart, arteriosclerosis of the aorta and an arteriosclerotic aneurysm of the innominate artery. Blood and cerebrospinal fluid showed neither increased pressure nor abnormal protein or cellular content. The EEG showed a background pattern of alpha activity with a localized left central, parietal and occipital spike focus, the spike activity being followed by delta waves in the same location. Left carotid angiogram showed no displacement of the middle cerebral vessels which were well filled, the wall of the internal carotid artery was unusually wide and straight and two filling defects in the lumen were interpreted as atherosclerotic plaques.

She was observed in hospital for eight weeks without further symptoms and was discharged to the neurological out-patient department where she has not complained of further symptoms.

These clinical observations have led us to conclude that while post-epileptic paralysis may occur without demonstrable cerebrovascular disease (Cases 4, 7, 8 and 9), in the presence of cerebrovascular disease seizures of short duration may provoke severe paralysis. Furthermore, there is evidence that in some of our cases (Cases 1, 2, 3, 5 and 6) the seizures themselves were probably the result of cerebrovascular disease.

Electroencephalographic Observations

Typical samples of EEG records made during and after seizures are shown in figs. 1 and 2. The samples illustrated in fig. 1 were made from two elderly patients with epilepsia partialis continua followed by post-epileptic paralysis (Cases 5 and 6). The records shown in fig. 2 were from two children with recurrent seizures followed by post-ictal stupor and confusion (Cases 7 and 8). In the EEG records slow waves were the most common concomitant of post-ictal paralysis. When the paralysis was limited to one side (i.e. post-ictal monoparesis or hemiplegia) the slow activity was limited to or showed preponderance in records made from central regions of the head opposite the paralysed side. In less localized paralytic states such as post-ictal coma or stupor the slow waves were correspondingly more diffuse. In confusional states following unilateral or bilateral temporal lobe seizures the slow activity commonly showed unilateral or bilateral temporal lobe preponderance. The phase in which the EEG is isoelectric, called the phase of "exhaustion or extinction" by Penfield and Jasper (1954), was not an invariable finding but was present in two of our records (1B, 2B).

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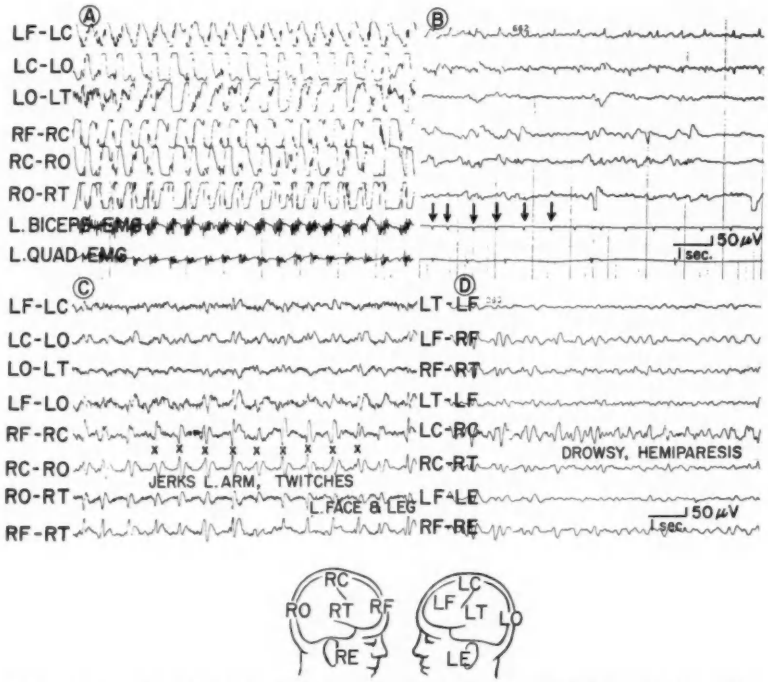

FIG. 1.—Samples of EEG records from two patients with epilepsia partialis continua and post-ictal paralysis due to cerebrovascular disease. A and B were recorded during and at the end of a typical seizure in a 68-year-old male with generalized atherosclerosis resulting in gangrene of the leg and thrombosis of the right middle cerebral artery five years earlier, from which there was good recovery. The onset of repeated left-sided seizures resulted in left hemiplegia between attacks. When the seizures were controlled he again recovered. Lower 2 channels show electromyograms recorded from left biceps and left quadriceps. Upper 6 traces show bipolar EEG records. In A, the spikes are diffuse but show right hemisphere preponderance, the muscle twitch responds to each spike. In B, the spikes are decreasing in amplitude and minimal EMG response is recorded (shown by arrows). C and D are samples of record from a 79-year-old male shown at necropsy to be suffering from arteriosclerotic occlusion of both middle cerebral arteries. Right hemiparesis had been present for two years, and left-sided seizures for two days. Each seizure, as shown in C, continued for 1–3 minutes and was then followed by additional left hemiparesis and stupor as shown in D, prior to the next seizure. During the interseizure period gradual recovery from left hemiparesis would occur. X indicates a jerk of left arm and twitches of left face and leg marked on record during seizure.

In our records during epilepsia partialis continua variations in the amplitude of the action potential recorded from the muscles of the convulsing limbs paralleled those of the cortical spike. Similar observa-

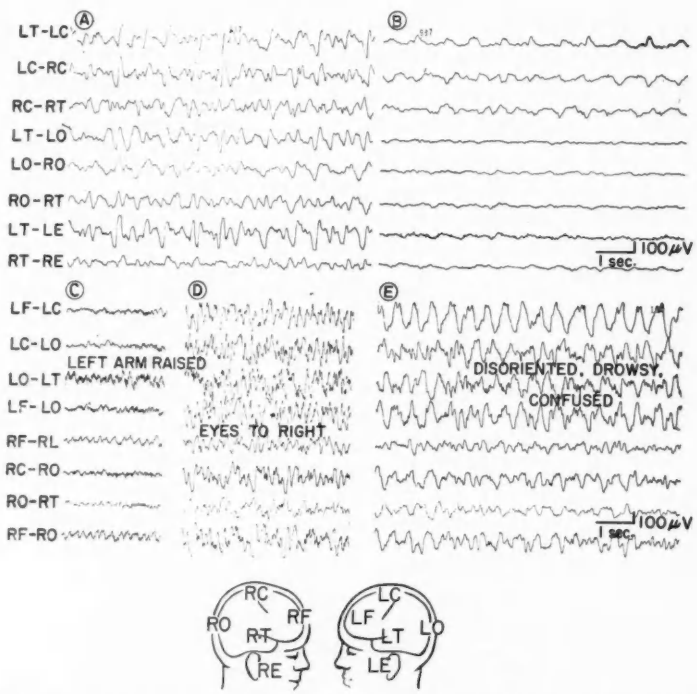

FIG. 2.—A and B are samples of a continuous EEG recorded from a 3-month female infant suffering from status epilepticus of five days' duration. The seizures were generalized clonic convulsions with tonic extension of neck and spine to two to four minutes' duration. A shows a typical seizure with diffuse discharges having left temporal preponderance. B, during post-ictal stupor there was flattening of the record in the left temporal region with slow waves elsewhere. C, D and E are samples of a continuous EEG recorded from a 5-year-old child with seizures for one year characterized by episodes of staring, raising the left arm and deviation of the eyes to the right with falling and unresponsiveness. C was made at the beginning of a seizure when spike activity was present in left posterior temporal region and the left arm was raised. In D, the spike activity was spreading predominantly in the left hemisphere. E was made during post-ictal confusion when high voltage slow waves were present over the left hemisphere.

tions have been reported in a case observed by Kugelberg and Widen (1954). At the beginning of post-epileptic paralysis the cortical spike potentials showed progressive reduction in amplitude until they were barely recognizable and were then replaced by slow activity or flattening of the record. At the stage of low-voltage spikes weak action potentials were barely recognizable in the EMG of the paralysed limbs (fig. 1B). During flaccid paralysis all cortical spike activity and EMG potentials

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recorded from the paralysed limbs disappeared. In an additional case of epilepsia partialis continua not illustrated here, tactile stimulation of the hand during the stage of recovery produced violent myoclonic jerks of the wrist and fingers (reflex epilepsy). However, during the early stage of post-ictal paralysis tactile stimulation had no effect.

The electroencephalographic data support the clinical view that long-continued localized or generalized spike activity eventually results in corresponding localized or generalized suppression of electrical activity with the appearance of slow waves. The slow waves are followed by gradual return of normal EEG activity at which time the cycle may repeat itself. During the stage of exhaustion the cortex is refractory to stimuli but it may become abnormally sensitive to stimuli in the stage of recovery.

Experimental Observations

Methods

Acute and chronic experiments were designed to test the hypothesis that post-epileptic paralysis is due to cerebral anoxia resulting from failure of the cerebral blood supply to meet the increased metabolic requirements during seizure activity. Experiments were performed in the cat and monkey. For purposes of comparison an area of relative cerebral ischæmia was compared with one having intact blood supply. This was accomplished by occluding one middle cerebral artery with a silver clip which permitted the effects of localized and generalized seizures to be compared in the normal and ischæmic hemispheres. Since the purpose of the acute and chronic experiments were different the methods used will be described separately.

Chronic Experiments

In 5 monkeys the middle cerebral artery was occluded using aseptic technique after reflecting an osteoplastic bone flap and inserting a sterile window in the skull so that the pial circulation could be observed (Meyer, 1959*a*; Meyer and Portnoy, 1958). In addition, a decompression was performed on the opposite side and stimulating electrodes made of 40 gauge enamelled steel wire were implanted in the lateral motor cortex of each hemisphere and were connected to four terminals of a small socket (amphenol connector) which was sealed into a hole in the skull with plastic cement (fig. 3). With this arrangement either one or both hemispheres could be stimulated in the unanæsthetized animal after attaching a plug with wires leading from a Grass stimulator. In this manner the effects of unilateral and generalized seizures could be observed in the same animal repeatedly.

After occlusion of the middle cerebral artery collateral blood flow was optimally maintained by preventing a fall in blood pressure and by the use of heparin. The animals showed little, if any, functional deficit seven to ten days following vascular occlusion, but previous studies have shown that they are subject to transient hemiplegic attacks by any stimulus which tends to upset the precarious balance between circulatory supply and local metabolic demand (Meyer, 1959*a*). On repeated occasions, seven to twenty-one days after surgery, the animals were subjected to alternating unilateral and generalized seizures and comparison was made of the duration of the post-epileptic paralysis produced by stimulation of each hemisphere. In all experiments continuous 16 mm. motion pictures were made so that the results could be reviewed and compared with other experiments. Observations of the pial circulation were also made through the skull window and in two experiments photomacrographs were made at a magnification of thirty times before and after the seizure and during the paralytic stage. Measurements of stimulation threshold were

made in several experiments before and during the paralytic stage. After three to four weeks' observation the animals were sacrificed and the brain was fixed in situ by perfusion with 10 per cent formalin and saline. Following fixation, each hemisphere was embedded in paraffin and comparable sections of "control" and "ischæmic" hemispheres were stained by hæmatoxylin and eosin and Nissl stains and examination with the microscope was made for any recent pathological change that might have resulted from the seizure.[1]

Acute Experiments

In 11 cats, the middle cerebral artery was occluded near its origin from the circle of Willis under local (xylocaine) anæsthesia and immobilization with repeated injections of D-tubocurare (0·5 mg. per pound). Artificial respiration was maintained at a constant rate with a Harvard respirator and a tracheal cannula. The cerebral cortex of each hemisphere was exposed and covered with a thin layer of mineral oil warmed to body temperature. After collateral blood flow was established on the ischæmic side experiments were performed to compare the cortical oxygen tension, pH, blood flow and EEG of the two hemispheres during seizures induced by electrical stimulation, intravenous injection of metrazol and by the application of strychnine sulphate to the cortex. In none of these experiments was there cortical infarction as judged by observation of the pial circulation.

Concurrent measurements of cerebral oxygen tension, EEG, pH and cortical blood flow measured with a thermistor were made together with the femoral blood pressure. These parameters were recorded with an 8 channel Offner ink-writing oscillograph, four channels of which were modified for direct current recording by use of Type 9138 input couplers. Blood pressure was recorded by means of a Statham pressure transducer.

Cortical oxygen tension was recorded by the electropolarographic method. Our adaptation of the polarograph (EPG) for recording oxygen tension of different areas of the brain with the Offner Type D dynograph (D) is shown in fig. 4 and will be described briefly. The polarographic method requires that a constant voltage of 0·6–0·8 volt be applied between a platinum cathode and a non-polarizable reference electrode (silver-silver-chloride or calomel half-cell) placed in the tissue to be examined (Davies and Brink, 1942). Changes in current flow depend on changes of oxygen tension in the tissues and may be continuously charted by a recording device placed in the cathode circuit. A resistor (R_1) is placed in the cathode circuit, from either side of which leads are taken to the dynograph which is converted to D.C. recording by Type 9138 input couplers (Offner Electronics, Inc.). A pen centering device (I) is incorporated into the input coupler which allows the use of maximum amplification without the necessity of further pen deflection. The impedance of the input coupler (R_D) is 75.000 ohms.

Under the conditions illustrated in fig. 4 changes in current in the polarographic circuit produce corresponding alterations in the voltage across R_1 and R_D (R_1+R_D). In this system, when the pen centering device is used, except at zero pen deflection, the voltage produced at the input coupler (I) is distributed between the impedance of the input coupler (R_D) and R_1 parallel with R_B. To minimize the voltage across R_B originating at I, R_1 should be small and the impedance of the input coupler large, thus causing most of the voltage to drop across the dynograph and not across the brain. In practice, with proper selection of R_1, the null balance voltage has little effect on the results, the voltage between the electrodes remaining between 0·6–0·8. Care must be taken, however, not to alter the voltage at I during any given experiment. For best matching of local impedance to that of the input coupler R_1 should be

[1]Dr. J. L. Chason, Professor of Neuropathology, Wayne State University, kindly supervised the preparation of these slides.

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small, but the minimum size of the resistor is necessarily limited by the minimum voltage change across this resistor which can be detected by the dynograph. We have found a resistance of 33,000 ohms to be optimum for our purposes. In order to plot the polarographic curve for normal saline illustrated in fig. 5 the amperage

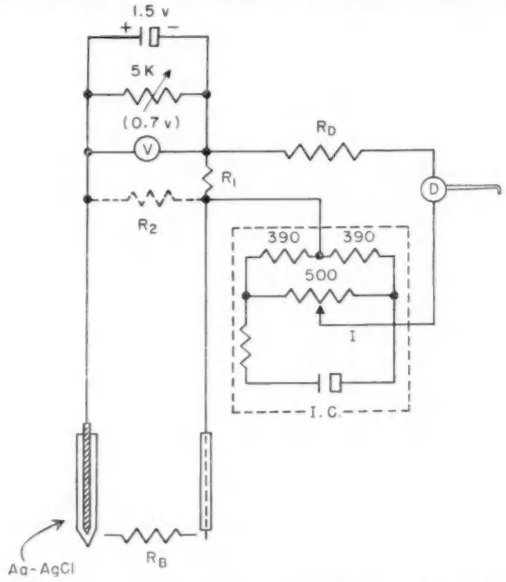

FIG. 4.—Circuit diagram to show adaptation of the polarographic method for recording oxygen tension by means of the Offner Type D, 8-channel dynograph. (*See* text.)

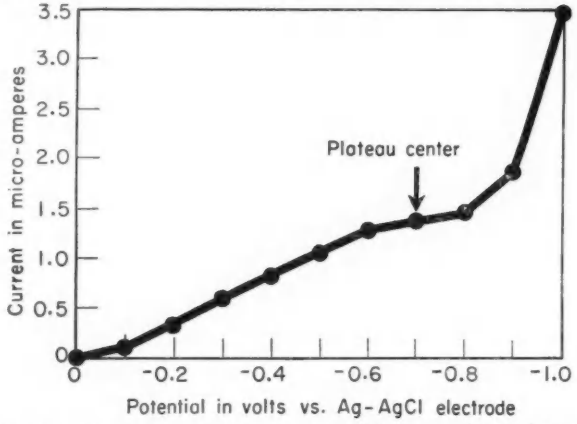

FIG. 5.—To show the plateau of the polarographic curve obtained by plotting the amperage at various voltages by means of the modification of the polarographic apparatus described in text.

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at the various voltages was determined by substituting calibrated resistors (R_2) for the polarographic electrodes. Since our main concern in the experiments reported here was with relative readings, absolute values of oxygen tension were not accurately determined but approximately zero oxygen levels were estimated at the end of each experiment by recording the reading of the brain after death caused by nitrogen breathing.

Changes in cortical blood flow were monitored with microthermistors inserted into the cortex and changes in pH were recorded with microglass pH electrodes (Sonnenschein *et al.*, 1953) and a Beckman pH meter (Model G) connected to the Offner polygraph. The EEG was recorded using bipolar electrodes separated by 5 mm. resting on the cortex on either side of the temperature, pH and oxygen electrodes. The validity of these methods has been discussed previously (Meyer and Denny-Brown, 1955). All electrodes were placed symmetrically on each hemisphere in order to sample the territory supplied by both the normal and occluded vessel for purposes of comparison. Continuous records were then made before, during and after seizures induced by electrical stimulation, by metrazol and by strychnine.

Results

Post-epileptic Hemiplegia

In all the chronic experiments a seizure limited to the ischæmic hemisphere or a generalized seizure resulted in transient paralysis of the limbs opposite the occluded middle cerebral artery (fig. 6). The paralysis varied in severity from a brachial monoplegia to hemiplegia and resulted from either a generalized seizure induced by stimulation of both hemispheres, by the intravenous injection of metrazol or by seizures limited to the ischæmic hemisphere induced by unilateral electrical stimulation or irrigation of the ischæmic hemisphere with strychnine solution. The duration of the paralysis varied directly with the duration of the seizure. The longer the seizure the longer the paralysis. Seizures lasting 45 seconds to 1 minute produced a paralysis of three to five minutes' duration. In one animal in which spontaneous epilepsia partialis continua arose from the ischæmic hemisphere and continued for ten days, post-epileptic hemiplegia persisted for twelve hours. In every instance the hemiplegia was of the flaccid type with absence or depression of tendon-jerks. The first sign of recovery was return of tone to the involved limb. Seizures of short duration (less than 45 seconds) produced paralysis limited to the fore-limb (fig. 6). Repeated short seizures or a single prolonged seizure resulted in flaccid hemiplegia with facial weakness, hemianopia and loss of response to painful stimulus on the paralysed side. Recovery occurred rapidly, usually in a matter of minutes with return of normal reflexes and tone on the involved side.

Prolonged generalized seizures of two to five minutes' duration produced a transient, flaccid quadriparesis for 10–25 seconds before return of function occurred in the limbs opposite the "control" hemisphere but hemiplegia always persisted for several minutes thereafter in the limbs opposite the occluded middle cerebral artery.

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During the stage of post-ictal hemiplegia the threshold voltage required to produce movement by stimulation of the paralysed hemisphere was found to be five times greater than that required to produce movement by stimulation of the intact hemisphere. With recovery from hemiplegia the threshold voltage returned to the same values in both hemispheres. In one animal as the stimulation threshold returned to normal after recovery from paralysis a transient decrease of threshold was demonstrated since myoclonic jerks could be precipitated in the formerly paralysed limbs by a number of sensory stimuli applied to the involved side including pin-pricks, tapping the tendons with a reflex hammer or flashing lights in the eyes. Such stimuli produced no response during the stage of post-ictal paralysis.

Another observation of interest was that in the active animal that had recovered from occlusion of the middle cerebral artery when equal voltages were applied alternately to each hemisphere, stimulation of the ischæmic hemisphere usually produced a more prolonged seizure and after-discharge than resulted from a similar stimulus applied to the "control" hemisphere.

It was regularly observed that rapidly repeated seizures of 10 seconds' duration produced a paralysis of cumulatively longer duration than resulted from a single seizure. For example, in one animal an initial 10-second stimulus produced a seizure followed by a monoparesis of 20 seconds' duration, the fifth produced a hemiplegia of 65 seconds' duration and the tenth stimulus produced a hemiplegia of 150 seconds' duration. Stimulation of the intact hemisphere did not produce observable post-ictal paralysis unless continued for 30 seconds or longer and when recovery was complete within 10–30 seconds (fig. 7) more prolonged stimulation of the intact hemisphere never produced hemiplegia of comparable degree or duration to that seen following stimulation of the ischæmic hemisphere for briefer intervals.

Pial Circulation During Seizures and Post-ictal Hemiplegia

Observation of the pial circulation through the skull window before, during and after a seizure with the dissecting microscope showed that 15–20 seconds after the onset of a seizure there was a steady increase in the width of pial arterioles which became visibly pulsatile. Maximum vasodilatation occurred in pial arterioles of 20–100 μ in width which doubled their width 1–2 minutes after the seizure had begun. In spite of the increase in arterial flow the venules and veins remained dark blue. Increased pial blood flow persisted during the stage of post-ictal paralysis (fig. 8) and gradually subsided in the ensuing 3–5 minutes. Active blood-flow without stasis continued at all times in the functionally paralysed cortex but the venous side of the circulation appeared cyanotic.

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Neuropathological Observations

Examination of the brain of these animals at necropsy showed that the middle cerebral artery had been occluded by the silver clips in all instances. The animals were sacrificed three to four weeks after occlusion of the middle cerebral artery and brain sections were studied microscopically to note if any recent neuronal changes were present due to the repeated seizures. Such recent changes were found; and they appeared to be due to the recent seizures rather than to ischæmia produced by vascular occlusion several weeks earlier. The changes consisted of pallor nerve cells, marked loss of Nissl substance and a pale, homogenous, eosinophilic appearance of cell bodies in the hæmatoxylin and eosin preparations. Most severe changes were found in one animal in which epilepsia partialis continua had been present for ten days prior to sacrifice. In this animal the pallor of nerve cells was so marked in the Nissl sections that the areas of pallor could be noted in the cortex with the naked eye. Though changes were noted bilaterally, in every instance the maximum changes were in the distribution of the occluded middle cerebral artery particularly in the parietal, temporal and frontal cortex. Less marked changes were also present in the intact hemisphere of two animals in whom prolonged seizures had been induced and in both of these the changes were present in frontal cortex in the distribution of the anterior cerebral artery.

Cerebral Blood Flow, pH, EEG and Oxygen Tension During Post-epileptic Paralysis

In the acute experiments concurrent observations were made of cortical blood flow, pH, EEG and oxygen tension during the state of exhaustion following seizure activity produced by metrazol, electrical stimulation and strychnine. Strychninization of the cortex was found to be the most satisfactory method of recording localized and generalized seizure activity with a minimum of stimulation or movement artefact. 10–20 per cent strychnine solution in saline was applied repeatedly to the cortex and in some experiments 1 ml. was injected intravenously in addition. Records of the effect of seizures induced by bipolar stimulation at a frequency of 60 pulses per second (10–40 volts, square-wave stimulus having a 1 millisecond delay) were made with the amplifying system attenuated during the period of electrical stimulation, and only the after-discharge was recorded. In spite of great increases in blood pressure and cortical blood flow as recorded by the thermistor (T in fig. 9A) cortical oxygen tension fell in both hemispheres (EPG 1 and 2 in fig. 9A). We have assumed the pattern of change during stimulation by comparing the record between the "ON" and "OFF" signals, the cortical temperature remained elevated for several minutes after the blood pressure had returned to normal levels indicating cerebral vaso-

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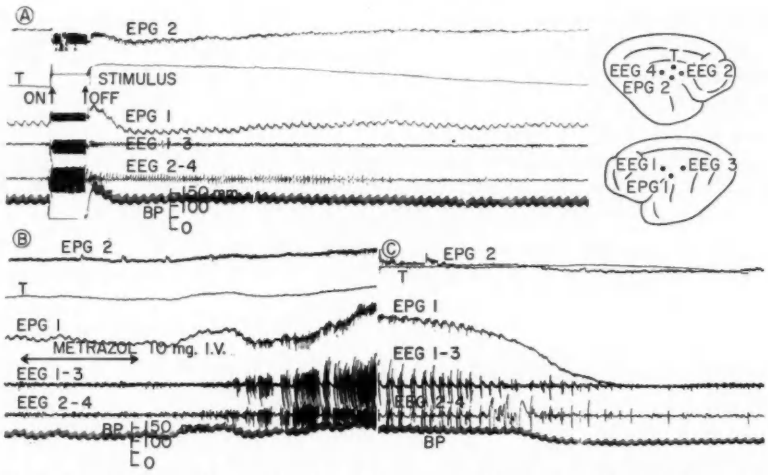

FIG. 9.—Concurrent records of cortical oxygen tension (EPG), blood flow (T) and blood pressure (BP) made during seizures produced in the same animal by electrical stimulation in A, and by metrazol in B and C. Electrode positions are shown to right of A. The left middle cerebral artery had been occluded. A, Electrical stimulation for 10 seconds indicated by ON and OFF produced a fall in oxygen tension (EPG) of both hemispheres but greater in the ischæmic hemisphere (EPG 1), in spite of a rise in blood pressure and cortical blood flow (T). B, After recovery 10 mg. metrazol I.V. produced spikes of 750 microvolts amplitude, a rise of B.P., and increased cortical blood flow (T) and oxygen tension (EPG). C, Sixty seconds later the cortical oxygen tension on the ischæmic side became rapidly reduced (EPG 1) and the seizure stopped.

dilatation which was confirmed upon microscopic examination of the pial circulation.

Metrazol seizures regularly produced a large rise in blood pressure and cortical blood flow (T in fig. 9B) with a temporary increase in cortical oxygen tension (EPGs in 9B). After several minutes of seizure activity there was a reduction in the cortical oxygen tension of both hemispheres, and seizure activity ceased in spite of continued cortical hyperæmia as indicated by the thermistor (fig. 9C).

Cortical spikes during seizure discharges regularly reached voltages of 500 microvolts or more and consequently were superimposed as an unavoidable artefact on the oxygen and pH records. During sustained after-discharges following electrical stimulation, and when prolonged seizures occurred after metrazol, seizure activity ceased when the oxygen tension fell to low levels. When the seizure had subsided, and if the oxygen tension remained low, the EEG became flat or showed a few scattered spikes and slow waves.

The dependence of the cortical seizure-discharge upon adequate

cortical oxygen tension was best demonstrated by strychnine seizures which tend to occur in alternating bursts followed by quiescence, and allowed an ideal preparation for this type of study (figs. 10 and 11). During strychnine seizure activity the cortical oxygen tension fell to near zero levels (as determined by dead brain at the end of the experiment) at this point cortical spike activity ceased and the EEG record became quiescent. The importance of the cortical oxygen tension in maintaining seizure activity was also shown by brief nitrogen breathing which

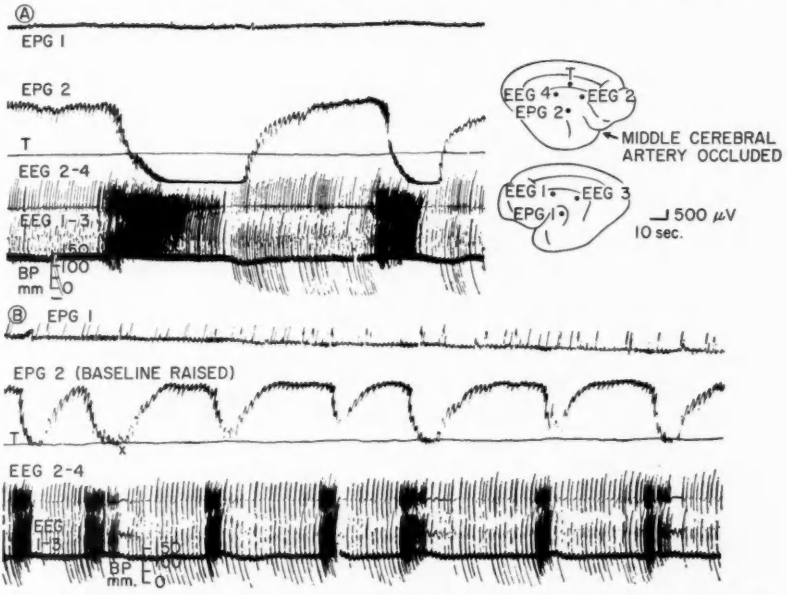

FIG. 10.—Two samples of a continuous record made in a cat to show the relationship of periods of epileptiform discharge alternating with depressed cortical activity, to cortical oxygen tension. The right middle cerebral artery had been occluded and strychnine solution applied to the right hemisphere. A, Rhythmical spikes suddenly increased in frequency and resulted in a seizure discharge arising in the right hemisphere (EEG 2–4) with rapid bilateral spread. With each seizure the cortical oxygen tension of the right (ischæmic) hemisphere was reduced to near zero levels, the seizure then ceased followed by a brief period of depressed cortical activity. The oxygen tension then increased and when it had returned to resting levels the seizure cycle began again. B, The baseline of EPG 2 was raised between A and B to record the fall of oxygen tension to low levels marked by point X at the end of the second seizure. After multiple seizures the oxygen tension of the normal hemisphere (EPG 1) began to be decreased and cortical blood flow (T) of the ischæmic hemisphere gradually increased. Electrode position and calibration of EEG and time are shown to the right of A and blood pressure calibration in the left lower corner of records A and B.

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terminated the spike activity and by breathing pure oxygen which prolonged it.

Strychninization of the cortex also permitted the study of predominantly unilateral seizures, although whenever strychnine produced high voltage, repetitive spikes in one hemisphere the seizure-discharge was soon recorded from homologous areas in the opposite hemisphere. Application of strychnine to the ischæmic hemisphere produced a seizure-discharge which regularly caused the oxygen tension to fall to near zero levels with cessation of spike activity. After the seizure ceased there was a rise in oxygen tension with a return of spike activity as the oxygen

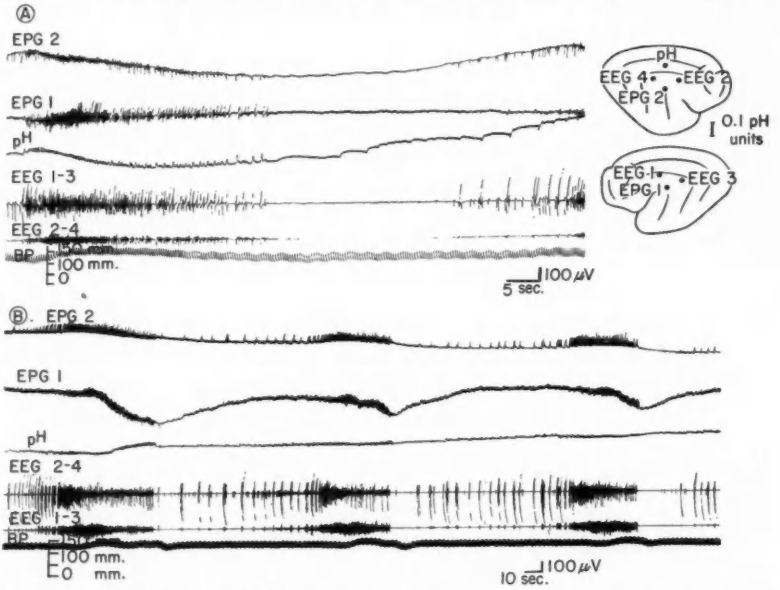

FIG. 11.—Samples of records from two similar experiments in different cats to show the dependence of the cortical seizure discharge upon the cortical oxygen tension. The electrode placements were the same in both experiments and in both the right middle cerebral artery had been occluded. A, Strychnine solution applied to the right (ischæmic) hemisphere has resulted in bilateral high amplitude spike discharges which produced a reduction of oxygen tension (EPG 2) and pH of the ischæmic hemisphere but not of the intact hemisphere (EPG 1). As the oxygen tension in the ischæmic hemisphere approached low levels the spikes decreased in amplitude and frequency and then ceased. As the oxygen tension rose the seizure discharge reappeared in both hemispheres. In this experiment the cortex became more acid at the onset of the seizure. B, Strychnine solution applied to both hemispheres produced bilateral seizure discharges with a fall in oxygen tension in both hemispheres resulting in cessation of the seizure, followed by a rise in the cortical oxygen tension and the cycle repeated itself. In this experiment the oxygen tension of the ischæmic hemisphere (EPG 2) was low at the start of the record.

tension approached the steady state, thereafter the cycle would repeat itself until the experiment was terminated (fig. 10). In several experiments such a repetitive cycle was recorded for four to five hours. Application of strychnine to both hemispheres or the intact hemisphere commonly produced longer sustained seizures resulting in the same cycle of events in both hemispheres, but recovery was often incomplete in the ischæmic hemisphere with resulting progressive hypoxia (figs. 10, 11).

During the stage of post-seizure cortical hypoxia with flattening of the EEG loud sounds failed to produce spike responses in the strychninized animal, but as the cortical oxygen tension rose loud sounds produced spike responses similar to those seen prior to the stage of post-ictal paralysis and by this means a seizure-discharge could be induced. Indeed, this phenomenon (the combination of sound and strychnine stimulation) was found useful in initiating cyclic repetition of the seizures.

Intermittent spike activity without sustained repetition characteristic of the seizure discharge produced small fluctuations in cortical oxygen tension and pH without producing sufficient cortical anoxia to cause quiescence of electrical activity. Occasionally single spikes occurred at intervals of a few seconds for as long as 30–40 minutes without interruption.

Discussion

Clinical Considerations

In the clinical studies described here the term status epilepticus has been used to denote recurrent generalized seizures without recovery of consciousness. Rhythmicity of seizures alternating with coma is characteristic of status epilepticus and the interval of seizure activity is seldom longer than two to four minutes in duration. Epilepsia partialis continua is not so easily defined (Koshewnikow, 1895; Spiller and Martin, 1909; Wilson, 1929). Our observations differ from those of Wilson who was of the view that absence of post-epileptic paralysis was characteristic of this condition. We have used the term to denote seizures limited to a limb, part of a limb or limited to one half of the body which persist for longer than one hour and are not associated with loss of consciousness although drowsiness may occur. We have seen cases of epilepsia partialis continua which have persisted for as long as two weeks. In general, the more localized the seizure (e.g. those limited to fingers and thumb) the longer the seizure persists without interruption but in all the cases we have observed there has been waxing and waning of the seizure activity and usually there has been intermittency, although this is not as evident as in status epilepticus. Some cases have features of both status epilepticus and epilepsia partialis continua (Case 4) since prolonged localized seizures may spread and become generalized, we classify such cases as status epilepticus.

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In cases not reported here, we have observed that when a prolonged seizure results in cyanosis or asphyxia the seizure is likely to terminate and recur when an adequate respiratory exchange is restored. Such data suggests that in man as well as animals the rhythmicity of prolonged seizures is influenced by the cortical oxygen tension.

In reviewing our own clinical experience of post-epileptic paralysis and comparing it with the description of others it is clear that post-epileptic paralysis may have many manifestations as well as numerous causes. Probably all severe generalized seizures are followed by some degree of diffuse cortical exhaustion varying from transient coma or stupor to drowsiness and confusion. For a short time after a generalized seizure bilateral grasp reflexes and extensor plantar reflexes are commonly found. Localized seizures, or more generalized seizures which preponderantly involve one part of the brain commonly result in transient neurological deficit clearly referable to the part of the brain most involved by the seizure. Thus, in severe unilateral frontal lobe seizures transient hemiplegia may be found while less severe attacks result in hemiparesis. If the parietal cortex is involved transient contralateral sensory loss may be demonstrable in addition (Case 1) and if the occipital lobe is involved hemianopia or visual agnosia may follow (Case 2). Temporal lobe discharges are commonly followed by states of confusion, disorientation and drowsiness and in such cases the EEG is helpful in demonstrating that this region on one or both sides shows a preponderance of abnormal activity compatible with neuronal exhaustion.

While it is clear that unusually prolonged or rapidly recurring seizures characteristic of status epilepticus commonly give rise to post-epileptic paralysis in the absence of vascular disease there are cases in which the seizures are relatively brief and the post-epileptic paralysis of long duration (Cases 1 and 2). These are of unusual interest and require further explanation: it is believed that an area of relative cerebral ischæmia due to vascular disease predisposes this portion of the brain to post-epileptic exhaustion paralysis.

During seizure activity the cerebral metabolic rate of oxygen is greatly increased (Schmidt *et al.*, 1945) and an area of relative ischæmia which is barely able to meet its tissue metabolic demand during normal activity may be unable to do so during the increased metabolic demand imposed by a seizure. This situation could result in local anoxia with accompanying paralysis of function. The arteriographic findings in 3 of our cases (Cases 1, 2 and 3), the necropsy findings in one (Case 6) and abundant clinical evidence in another support such a view since the vessels supplying that area paralysed by the seizure were demonstrated to be abnormal.

It is not intended to imply that in all cases of post-epileptic paralysis vascular disease is present. In Case 4, for example, there was neither

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clinical nor arteriographic evidence of vascular disease. We wish to emphasize, however, that impaired circulation of the brain predisposes the individual to post-epileptic paralysis.

The Nature of Post-epileptic Paralysis

The experimental studies described here indicate that post-epileptic exhaustion paralysis is due to temporary neuronal anoxia. In the presence of intact cerebral circulation longer seizures are required for the increased neuronal demand for oxygen to outstrip the available supply than when cerebrovascular insufficiency is present. In either instance the cortical supply of oxygen is exhausted in spite of increased cerebral blood flow which normally accompanies a seizure. During the state of anoxic neuronal paralysis the cortical stimulation threshold is increased by five times that of normal cortex. Cessation of the seizure due to reduction of neuronal excitability results in abrupt reduction of the cerebral metabolic rate and the cortical oxygen rises toward the steady state. The cortical stimulation threshold returns to normal as the oxygen tension rises and may become lowered with a tendency to excessive discharge. Seizure activity is likely to begin again and the EEG shows that periods of seizure discharge alternate with electrical quiescence, the rhythmicity apparently being dependent on the cyclic rises and falls of cortical oxygen tension. It may be inferred that toward the end of a seizure the available cortical oxygen is exhausted and the neurones cease to discharge, as the oxygen is replenished the seizure begins again and the cycle may be repeated many times.

Effect of Seizure Activity on Vascular Insufficiency

In the unanæsthetized monkey which has recovered from occlusion of the middle cerebral artery generalized seizures or seizures localized to the ischæmic hemisphere regularly produce hemiplegia. This results from failure of the tenuous blood supply in the ischæmic area to supply the increased tissue demand for oxygen during the seizures. When the seizure ceases the rate of recovery depends on the severity and duration of the seizures. Resulting paralysis can thus vary from a few seconds to several days in duration. If seizures are sufficiently prolonged irreversible neuronal damage occurs with accompanying structural change recognizable on microscopic examination.

Summary

(1) Post-epileptic paralysis may vary in its manifestations from diffuse signs of cerebral paralysis such as stupor and coma to localized signs of neurological deficit such as hemiplegia, hemisensory disorder and hemianopia. Signs of exhaustion of the temporal lobe include impaired memory, disorientation and confusional states.

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(2) Post-epileptic paralysis may occur after prolonged localized or generalized seizures in the absence of demonstrable cerebrovascular disease but cerebrovascular insufficiency predisposes to post-epileptic paralysis and when present seizures of brief duration tend to result in prolonged neurological defect. If an area of cerebral ischæmia exists a generalized seizure results in a localized neurological deficit referable to the ischæmic area.

(3) Continuous electroencephalographic records made during seizures and post-epileptic paralysis show that slow waves or absence of electrical activity are characteristic of the stage of post-epileptic paralysis. Such abnormality is usually diffuse after generalized seizures and localized after focal seizures, in which case it is found in that area of brian involved by the seizure. Following temporal lobe seizures the EEG is helpful in showing that abnormal activity is still present in the temporal regions. Epilepsia partialis continua is commonly followed by transient post-ictal paralysis in those parts in which the limited convulsion occurred. At the end of a seizure the cortical spike activity and the resulting action potentials of muscles involved by the convulsions show a parallel decrease in amplitude. After the seizure neuronal excitability slowly returns and may be shown to be excessive prior to the onset of the next seizure.

(4) Experiments show that in the unanæsthetized monkey which has recovered from occlusion of the middle cerebral artery, seizures result in transient hemiplegia. During the paralytic stage the cortical stimulation threshold is increased, in the interval prior to the onset of the next seizure it is decreased.

(5) Concurrent records of cortical EEG, blood flow, pH and oxygen tension show that post-epileptic paralysis appears to be due to cortical anoxia resulting from the metabolic demand for oxygen outstripping its supply. Occlusion of cerebral vessels results in a tenuous balance between tissue supply and demand for oxygen and predisposes the ischæmic area to post-epileptic paralysis.

(6) Rhythmicity of prolonged, intermittent seizures characterized in the EEG by bursts of rapid spike activity alternating with quiescence appears to be mediated by corresponding rises and falls in cortical oxygen tension. The seizure exhausts available oxygen supply and there is neuronal quiescence until the oxygen supply is replenished.

We wish to express our gratitude to Dr. F. Morin who gave technical advice and aided in the experimental part of this study and for the technical assistance of Mr. Peter Miller.

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FIG. 3.—To show the head assembly for producing unilateral or bilateral seizures in the unanæsthetized monkey that had recovered from occlusion of the middle cerebral artery. A, Detail of head to show detachable plug assembly which connects stimulator with implanted electrodes placed in the motor cortex of each hemisphere. The skull window and skin flaps used during insertion of electrodes and occlusion of the middle cerebral artery are visible. B, Animal with stimulating electrodes plugged into head assembly prior to studying effects of unilateral and bilateral seizures.

To illustrate article by John S. Meyer and H. D. Portnoy.

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PLATE XIX

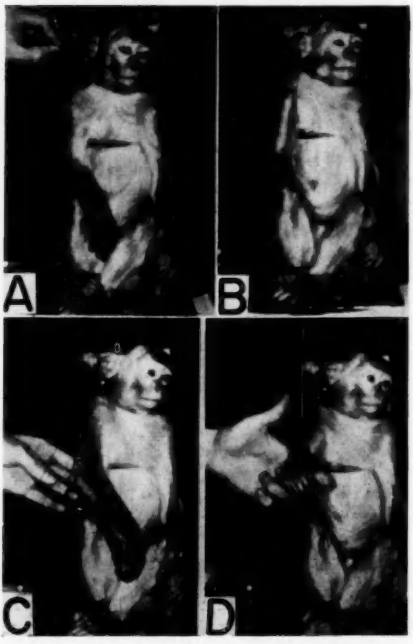

FIG. 6.—Series of photographs to show transient monoparesis of the right fore-limb produced by brief electrical stimulation of the left motor cortex in a monkey that had recovered from occlusion of the left middle cerebral artery. A, Control picture prior to stimulation. B, To show the unilateral convulsion of the right fore-limb produced by stimulation of the left motor cortex for 30 seconds. C, Twenty seconds after the stimulation was over a flaccid monoparesis was present. D, Forty-five seconds after the convulsion tone and strength were rapidly returning.

To illustrate article by John S. Meyer and H. D. Portnoy.

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FIG. 7.—Series of photographs taken of the same animal shown in fig. 6 to show that brief stimulation of the opposite, intact hemisphere failed to produce prolonged post-ictal paralysis. A, Control picture prior to stimulation. P, During stimulation of the right hemisphere there was a seizure localized to the left limbs and face. C, Twenty seconds after the stimulation was over no weakness was present.

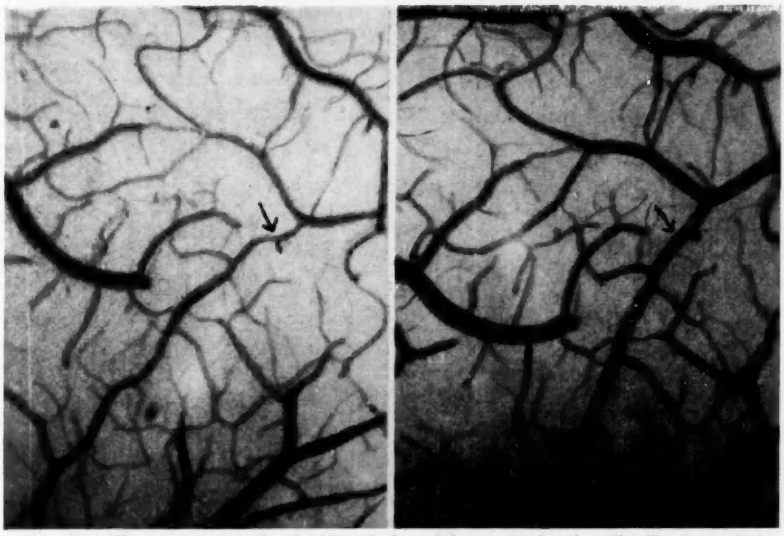

FIG. 8.—Photomacrographs (×30) of the pial vessels in the distribution of the occluded middle cerebral artery taken before and after a seizure to show vasodilatation without stasis during post-epileptic paralysis. The photograph to the left was taken before the seizure; that on the right was taken 30 seconds after the seizure, while the animal was paralysed. Arrows indicate the same arteriole which measured 50 mμ prior to seizure and 100 mμ after the seizure.

To illustrate article by John S. Meyer and H. D. Portnoy.

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EXPRESSIVE APHASIA AND AMUSIA
Following Right Frontal Lesion in a Right-handed Man

BY

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THE publications dealing with amusia are scanty, especially if compared with the great number of books and papers dealing with troubles of spoken or written language. This situation can be explained by the facts that in most of the published cases amusia appeared as a constitutive part of expressive or receptive aphasia (Weisenburg and McBride, 1935) and, on the other hand, that in routine practice we have no available "battery" of investigation tests for the examination of the musical functions.

Contrasting with most published cases of amusia in which severe aphasia and motor defect of hemiplegic type were always present, in the case under discussion the musical expressive functions (vocal and especially instrumental) were gravely affected whilst language and motor disturbances were almost totally absent at the time of the musical-function examination. Another particular aspect in our case is the location of the lesion in the apparently minor hemisphere of a right-handed, right-footed and right-eyed young man.

The application in this case, particularly propitious for a clinical study, of a personal test battery for the investigation of musical functions led to some interesting results.

Case Report

D. M., aged 26 (obs. No. 19, 686), was admitted to the Clinical Section of the "I.P. Pavlov" Neurology Institute ("Gh. Marinescu" Hospital), on July 11, 1958, for partial and generalized convulsive seizures. The patient had finished a five-year course in the elementary school. He is right-handed (hand, foot, eye). Moreover, our investigations proved him to be a congenitally true right-handed, and not a shifted sinistral type. His parents and grandparents were right-handed, whilst one of the seven brothers and sisters of our patient is left-handed and left-footed, but right-eyed.

The patient was a farm hand who used to play the accordion in a band. Before his illness he used to sing and play dance music and folk songs. He had never been at a music school and had had no musical training. He used to play the accordion since he was 9 years old.

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History.—He suffered from a skull injury in 1948; he was violently hit in the occipital area of the skull and lost consciousness for an hour. Two months later he began to have generalized epileptic attacks with loss of consciousness. At the same time, fits of a particular character, without loss of consciousness set in. He had the feeling that he was seeing the objects around him through a fog, he could not speak for one to two minutes, and felt the impulse to walk about the room for some more minutes.

In April 1950 he was admitted to the Neurosurgical Clinic. The pneumoencephalogram showed a slight displacement of the ventricular system to the left. A brain parasitosis was suspected, and the patient was operated upon (right fronto-temporal craniectomy, Dr. C. Arseni). The dura mater had a normal aspect. There was a slight leptomeningitis in the area of the Sylvian fissure, but no sign of cerebral parasitosis. After this negative exploration, the neurological state of the patient became normal. After 1951, epileptic seizures appeared every three to four months. After barbiturate treatment the interval between the seizures increased. At the same time the patient also had *petit-mal* seizures without loss of consciousness which lasted for one or two minutes. In these the head and eyes turned suddenly to the right and if he happened to be standing, he started turning round from left to right. In other instances, there was a sudden stop in the patient's conversation (total arrest of speech or seizures of verbal repetition). During all these seizures he was perfectly conscious, understanding every word spoken to him. In 1955 and 1956 the frequency of the *petit-mal* seizures increased (sometimes 3–4 seizures daily). In February 1957 he had his first seizure with arrest of inspiration lasting 15–20 seconds. Later, he had seizures consisting of a deep inspiration or expiration followed by an inability to perform the next movement of breathing. These respiratory seizures lasted for a few seconds and were sometimes accompanied by an increased pulse-rate (up to 120). There was no abnormal change of temperature, but the blood pressure appeared to rise (the maximal increase was from 130 to 160 mm.Hg).

The seizures of arrest of speech or verbal repetition were sometimes accompanied by transient increases of the muscle tone of the left limbs followed by a transient paresis of the left shoulder. In other instances all these types of seizures could combine with or precede a generalized attack. The patient was again admitted to the clinical section of the I.P. Pavlov Institute. Skull roentgenogram showed a calcification in the right posterior frontal area (figs. 1, 2) following which he was transferred to the Neurosurgical Clinic.

EEG examination (Dr. C. Samitca) revealed a slow-wave focus in the right frontal region. *Operation*, May 16, 1957 (C. Arseni assisted by S. Ionescu and N. Pietraru). Total removal of a calcified oligodendroglioma of the posterior third of the first two frontal convolutions. The tumour, weighing 55 grammes, involved also the subcortical region of the posterior third of the third frontal convolution.

While on the operation table, the patient suddenly felt that he was not able to move the fingers of his left hand and, at the same time, could not utter a single word for some minutes. Afterwards he recovered his speech but expressed himself with some difficulty. After the operation there was a palsy of the left arm which disappeared within a few days. Moreover there were some dysphasic disorders of the expressive type with motor paraphasia, occasional difficulty in finding unusual words, a changing of the rhythm and pitch of the voice (prosodic qualities of speech). A most remarkable fact is that since his operation the patient has complained of not being able to earn his living as a musician because his singing was "wrong," and he could not play his accordion at all.

In the period following the operation there still occurred three paroxysmal vegetative seizures. There were no more seizures of arrest of speech or verbal repetition. However the convulsive attacks persisted and were accompanied by

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short *petit-mal* seizures. There was no important change in the patient's condition during the following period except the marked improvement in the left arm paresis and a slight improvement in the expressive speech troubles. The clinical examination performed four months after his last admission (October 1957) was as follows.

General neurological examination.—Gait normal. Slight diminution of muscular force in the left hand which shows some difficulty in performing skilled actions. The tendon reflexes are brisker in the left upper limb; the other tendon reflexes as well as the cutaneous ones show no abnormality. No Babinski sign. Slight hypæsthesia of the fingers and of the inferior third of the ulnar border of the left forearm. Left central facial paresis. No other neurological abnormality.

Speech examination.—The patient asserts that since the day of the operation his voice has changed: "Sometimes it is too weak, the words being sometimes too strong and quick, and at other times they are, on the contrary, too weak and slow. Now and then the words I'm pronouncing are distorted."

Spontaneous speech.—In ordinary conversations the patient frequently repeats the first two to three letters of some word. Condensation is frequent. Instead of putting the usual pauses between words, he condenses the last syllable of the first word with the first syllable of the following, omitting 2 or 3 letters. The patient is conscious of all these faults and tries to correct them. He asserts that before the removal of the tumour he used to speak quickly but fluently and correctly. Now there is a tachyphemy with difficulty in the terminal articulation of the word. When pronouncing a complicated word he omits some letter or syllable (e.g. "culral" instead of "cultural"). The patient can utter correctly the days of the week, and the months; he counts correctly.

Repeated speech.—This is normal for letters, syllables, words with and without sense, as well as simple propositions. Repetition of the phrases shows disturbances in the word-articulation and a slight tendency to use the telegraphic style. All these troubles are analogous to those described in the "spontaneous speech."

Naming of ordinary objects, colours, pictures representing objects or animals is satisfactory. However, there is a somewhat longer latent period for some less usual nouns (stamp, zebra, elephant). Recitation of poetry shows disturbances analogous to those described with the spontaneous speech.

Comprehension of spoken language.—The understanding of words, short sentences and longer phrases is not altered. The patient understands the stories and proverbs corresponding to his instruction level. If given quick and complicated verbal orders ("strike the table three times with your fist and put your left hand on your right eye and then on your right ear"), he confuses the whole performance or, after some initial mistake, corrects himself after repeating loudly the order or a fragment of it.

If the same order is given at a slow rate, the execution is correct. This slight disturbance of comprehension of spoken language is often present in frontal tumours of the major hemisphere and has been called by one of us (Botez, 1958) "verbal inattention."

Writing to dictation still produces an occasional literal error. Drawing is normal.

Reading shows disturbances of articulation which become more apparent when the patient reads a longer text.

Whispering (speech and reading) shows the same disturbances as those described with the loud-voice speech and reading.

No acalculia; no ideational, ideokinetic, constructional or dressing apraxia. There is no right-left disorientation; no Gerstmann syndrome.

The *mental state* is normal. The patient asserts that since the operation he has a tendency to forget, especially recent events.

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This examination included no testing of the musical functions. However, it was established that the patient was not able to sing correctly a tune he knew very well. He complained of this trouble asserting his singing was wrong.

A complete examination of the musical functions was performed in July 1958, a year after the operation.

Evolution and clinical examination in July 1958.—In the period following his last hospitalization, the patient had had 7 paræsthetic fits in the left side of the face (during this period he received a barbiturate treatment). There is no motor inability of the left hand: the patient is able to perform any complicated movement with both his hands and fingers. Slight facial paresis on the left. He complains of intonational disturbances; of the changing of pitch of his voice, of the inability to sing or play the accordion. The audiometric examination shows a moderate right hypoacusia of the mixed type.

Language examination.—Subjectively and objectively the patient's speech is much improved. There is an intonational defect, tachyphemy with a tendency to condensed expression. There is also a slight dysarthria. The terminal articulation of words shows no defect. There is no tendency to omit a letter or syllable in the more difficult words. No troubles of comprehension, writing, no dyscalculia.

Analysis of the prosodic quality of speech.—In a series of interesting papers, G. H. Monrad-Krohn (1947*a*, 1947*b*) discussed the prosodic quality of speech and its disturbances. He showed that besides vocabulary and grammar one has to consider also a prosodic quality of human language which gives to speech various shades of sense, by means of stress, pitch and rhythm variations. The analysis of the prosodic quality of our patient's speech proved to be of interest. Indeed, the stress (which depends on the amplitude of vocal emission) was distributed explosively, without any relation to the sense of the sentence. The pitch (which depends on the frequency of the sound) was of a remarkable monotony. The interval between the higher and deeper sound emitted by the patient whilst speaking never exceeded a minor third. (Grammont (1946) proved that in normal speech this interval should not be less than a fifth and at most an octave.) As to the rhythm, we observed that the patient used to omit the normal pauses between the successive words, prolonging the last syllable of a word and thus making a transition to the following word. In other instances, he condensed the words as shown by us (dysphasic element).

Examination of the Musical Functions

In order to investigate the musical functions of our patient we made use of an original battery of tests (Wertheim and Botez, 1959) which is based upon a precise classification of human subjects according to their musical aptitudes and training. Considering as very important the critical attitude of the patient to his own performances our "battery" allows us to distinguish the receptive (gnosic) element, from the productive (praxic) one. Our battery containing 45 tests allows a very fine and detailed investigation. However, our patient was an "empiric" musician who ignored musical notation and had no theoretical musical knowledge, and consequently there were a series of tests we could not apply in his case (solfeggio, musical dictation, transcription, nomination of the musical intervals, decomposition of chords, "time-beating" movements, etc.).

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I. Receptive and Mnesic Component

A. *Tonal, Melodic and Harmony Elements*

Appreciation of the pitch of sounds.—If given two successive sounds (emitted by voice or accordion), the patient appreciated their relative pitch correctly even if the interval between them was of only a semitone.

Reproduction of separate sounds.—(*a*) Emitted by voice: the patient reproduced correctly the separate sound emitted vocally in his usual register (fig. 3).

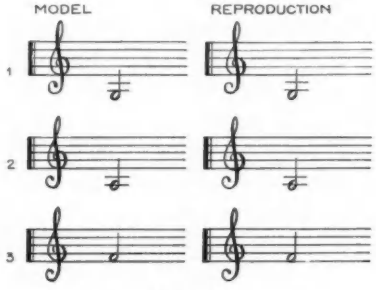

Fig. 3.

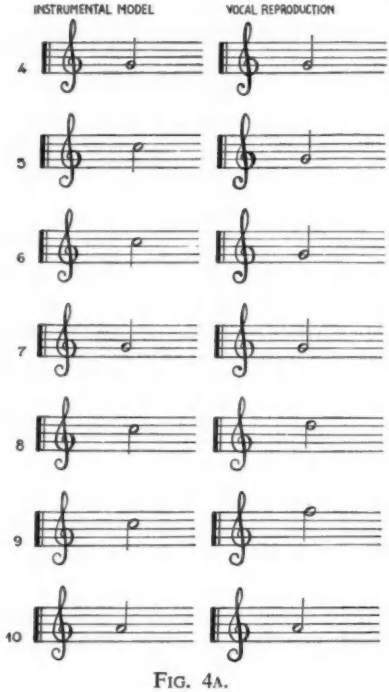

Fig. 4A.
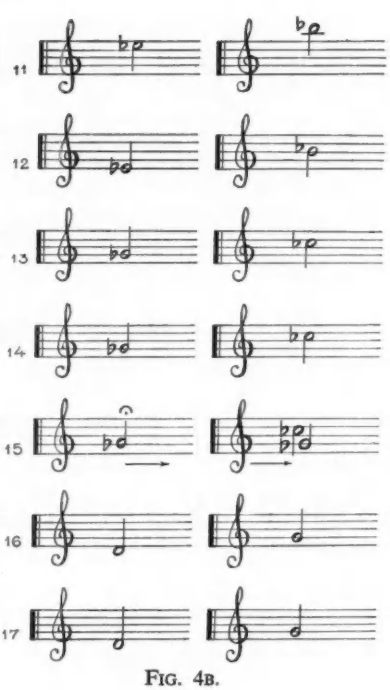
Fig. 4B.

(*b*) Sounds emitted by an accordion (fig. 4A and fig. 4B): the patient began by a correct reproduction of the G (ex. 4) but immediately afterwards he reproduced nearly all the "model" sounds by *transposing them to the superior or inferior fourth* (ex. 5, 6, 9, 11, 12, 13, 14, 16, 17). If the "model" sound was prolonged and the patient asked to reproduce it concomitantly he added the inferior fourth and thus the two sounds could be heard simultaneously (ex. 15). *The patient was perfectly conscious of each error he committed but was unable to correct it.*

If the examiner emitted *vocally* the D, the reproduction was again G, that is to say the superior fourth (fig. 5, ex. 18, 19).

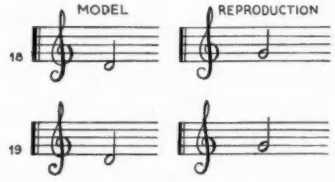

FIG. 5.

Recognition of a well-known melody.—The patient recognized without difficulty the tune "Perinita" which was sung for him (without text) as well as the waltz "The Waves of the Danube."

Recognition of intentional faults in a well-known melody.—The patient drew attention to an intonational fault (even if the mistuning was of only a semitone) but seemed not to be aware of the time faults. However, he appreciated as such the correct execution.

Numeric decomposition of a chord.—The patient specified without mistake the number of sounds in a chord with 2, 3 and 4 voices (major third, major third + perfect fifth, major third + perfect fifth + octave).

Differentiation of major and minor chords.—The patient distinguished a perfect major chord from its analogous minor without being able to explain the difference (by lack of elementary theoretical musical knowledge).

B. *Rhythmic Element*

Imitation (reproduction) of a rhythm, tapped with the reflex-hammer (fig. 6).—The patient handled the hammer without showing any praxic trouble but, as shown by the examples 20–24, reproduction of various rhythms was considerably deficient.

Reproduction with the reflex-hammer of a "sounded" rhythm (obtained by percussion of the G key of a piano) (fig. 7, ex. 25).

Reproduction with the reflex-hammer of the rhythm of a piano-played melody (fig. 7, ex. 26).

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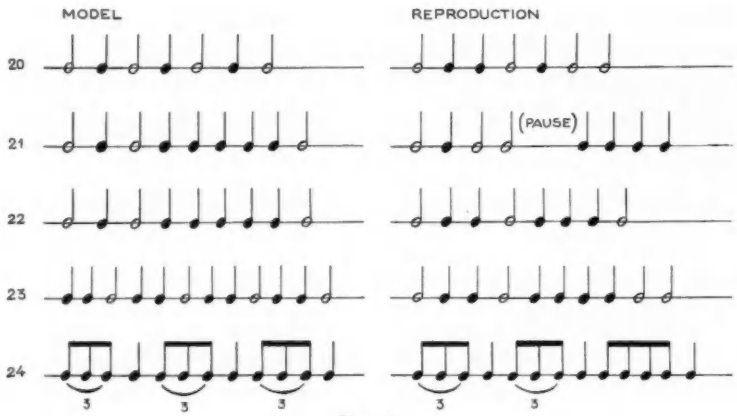

FIG. 6.

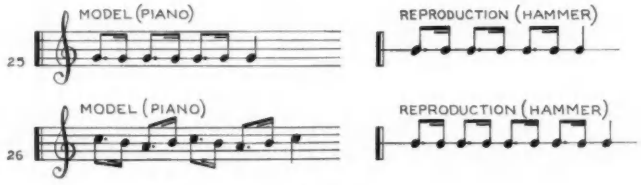

FIG. 7.

The ex. 25 and 26 show that rhythm reproduction became correct if the rhythm was "bound" to a sound or a series of musical sounds.

C. *The Agogical and Dynamic Elements*

Description of the time of a musical piece.—If the examiner sang or played for him several pieces, the patient could always tell which of them was slower or quicker.

Perception of tempo-variations.—The patient caught the ritardando or accelerando introduced into the piece which was played for him. He also observed and marked out the passage from a slow to a quick movement and vice versa.

Perception of dynamic variations.—The patient perceived and marked out the dynamic variations of the *crescendo* or *descrescendo* type which appeared in the piece played for him.

II. PRODUCTIVE COMPONENT

A. *Singing and Whistling Tests*

(*a*) *Tonal, Melodic and Harmony Elements*

Spontaneous singing of a well-known melody.—The patient began to

sing the popular tune "Foaie verde de sulfina." The performance had the following imperfections.

—intonational faults, especially in the first bars, which were corrected subsequently;

—stress faults regarding both the musical line and the text;

—here and there an abrupt (staccato) and tremolo intonation of long sounds.

Asked to sing spontaneously a dance-tune, the patient produced a melody with little intonational faults (especially at the beginning), but without any rhythmic character. Our patient's "dance-tune" was rather a sort of psalmody, impossible to be danced to.

Asked to express an opinion on his performance, the patient asserted that since he had been operated on (1957) he could no longer sing "in a sweet manner" and that he had sung wrongly both of the tunes. Questioned on the possibility of the tune sung by him to be danced to, the patient answered affirmatively which proved that he was not aware of the rhythmic faults in his own performance.

Spontaneous whistling of a well-known melody.—The patient told us that since the operation he could no longer whistle correctly. Trying to whistle the waltz "The Waves of the Danube" he obtained a vague, weak and tremolo sound-emission, most of the intervals being false.

Spontaneous singing with piano accompaniment.—Generally speaking, the performance was intonationally better than the unaccompanied one but there was a tendency to go too slow, and to lag behind on the accompaniment. Asked to appreciate his performance the patient said: "When I am accompanied I go too slow, and I'm retarding both the melody and the words."

Repeated singing.—The vocal reproduction by the patient of an unknown tune which was sung to him was intonationally deficient although there was still some resemblance to the model. The deficiency was still more marked if the model was played on the accordion instead of being sung. Besides the false intervals it is remarkable that in the patient's performance there was no rhythm at all (fig. 8, ex. 27).
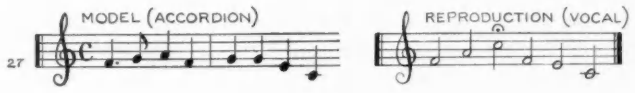
FIG. 8.

The vocal reproduction of a melody, familiar to the patient, was also deficient from the intonational and rhythmic point of view (fig. 9, ex. 28).

In the case of an unknown instrumental model, the reproduction showed great intonational and rhythmic alterations (fig. 9, ex. 29).

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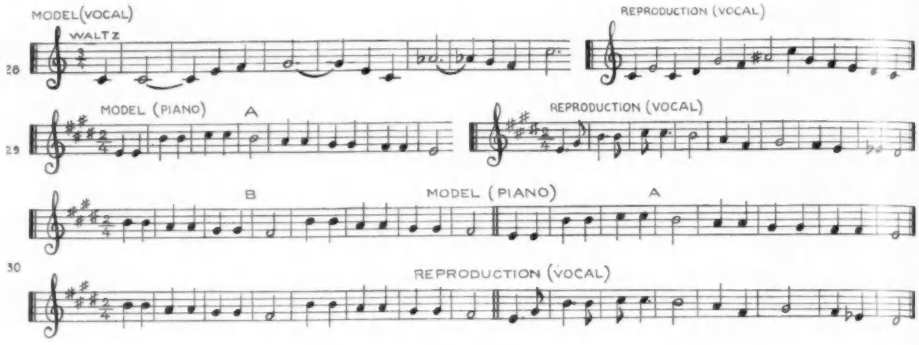

FIG. 9.

Thereafter (fig. 9, ex. 30) the patient was asked to reproduce the second part of the tune (B) and the "reprise" (A).

We may emphasize the fact that the part B (descending) of the tune was reproduced correctly whilst all the faults seemed to concentrate in the part A (ascending). This fact must be considered together with the result of another test (ex. 31–34).

The patient was deeply dissatisfied with his production but he could not improve it even if he repeated the tune several times.

Repeated whistling.—A few separate sounds were reproduced correctly whilst the repeated whistling of the ex. 28 was as deficient from the intonational and rhythmic point of view as was the vocal production. Here also the patient was perfectly aware of all his faults but was unable to correct them.

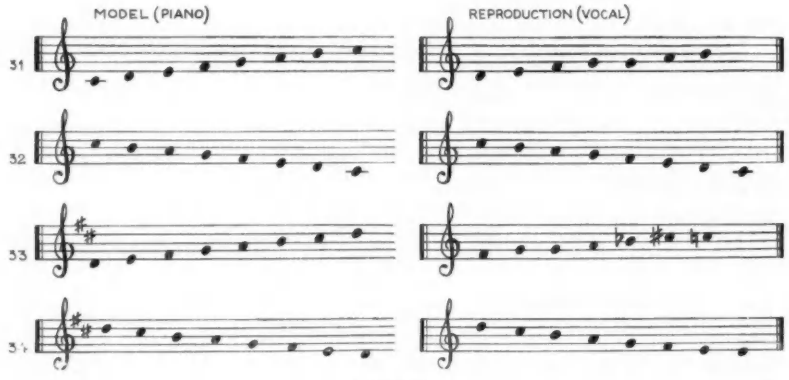

FIG. 10.

Vocal reproduction of an ascending and descending scale (fig. 10).—Our patient could not be asked to sing spontaneously a scale the theoretic notion of which was unknown to him. The repeating-test shows that the reproduction of descending scales (ex. 32, 34) was relatively good whilst in the ascending scales there were many mistunings, sometimes perseveration on the same note, introduction of chromatisms, etc. (ex. 31, 33).

This phenomenon was established constantly for all the tested keys (A major, H major, G major, C sharp major, etc.). With minor keys the mistunings were still more important, but the descending scale was correct as well.

The patient reproduced correctly the legato or staccato character of the model scale.

(*b*) *The Agogical and Dynamic Character*

Spontaneous singing accelerando and ritardando.—The patient was unable to perform the requested agogical variations.

Spontaneous singing crescendo and descrescendo.—The patient failed to perform the dynamic variations requested by the examiner (even if the latter gave him practical examples) or performed them in the opposite sense (he sang crescendo instead of the requested descrescendo).

B. *Instrumental Tests*

The instrument we used for our testing was somewhat simpler than the one on which the patient used to play before being operated upon. It was a Hohner accordion with 22 keys (two rows of 11 buttons) and 8 bass-keys (the patient's instrument had 12 bass-keys).

General manipulation of the instrument.—The patient correctly held the accordion sustained by its belt passed over his right shoulder. He knew which was the air-valve, but during the testing it was remarked that he used the bellows excessively, almost damaging the instrument.

Spontaneous playing.—Asked to play something, after a series of vain efforts to produce a melody, the patient at last succeeded in playing the beginning of a popular tune without being able to go farther than the two first bars, after which he missed the tonality and the sense of the melody was lost. The patient performed all this using only his right hand, without playing the bass. Asked to play only on the bass keys, the patient showed that he could play the usual harmony with his left *but was unable to play with both hands at the same time.*

Asked to play something else, the patient tried a piece he used to play mostly before the operation. He tried to play and then to sing. The vocal production was almost good, approaching a satisfactory level, whilst the accordion production was fragmentary and absolutely wrong. There was no resemblance to the tune the patient intended to produce. He had a perfectly critical attitude to his performance. Asked to explain

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his difficulties he asserted that he knew the keys he must press, but "the fingers did not carry out the order."

Repeated playing (reproduction).—The patient was unable to reproduce on his accordion even the simplest melody.

Polyphonic playing.—As we have shown, it was impossible for our patient to play anything bimanually. Asked to use both hands in playing, he played first with his right alone, then with his left alone.

Accompaniment by the patient of his own vocal production.—Since the patient told us that before the disease he frequently practised in his profession this form of musical performance, we decided to submit him to this test also. It revealed a most interesting fact: whilst the vocal part was almost correct from the intonational point of view, the "accompaniment" was totally chaotic, giving the impression of an arrhythmic and fully atonal production. A listener of the recording of this test (we had them all recorded on sound-tape) might have had the impression that in the room were two persons; a singing adult and a child who was *playing with* an accordion, casually pressing a button now and then. The most curious aspect of this dissociation was the fact that the total "atonalism" of the instrumental accompaniment did not in the least put off the patient, who continued his vocal part without deviating from the original key.

Discussion

The symptom-complex offered by our patient raises several problems; we shall especially discuss the dysphasic troubles and expressive amusia.

The seizures of arrest of speech or verbal repetition can be explained by compression or direct involvement of the pre-rolandic region and particularly the supplementary motor area by the tumour (Penfield and Welch, 1951; Penfield and Jasper, 1954; Guidetti, 1957). The paroxysmal seizures of hypertonia and the transient paresis of the upper arm muscles on the contralateral side to the lesion prove the involvement of this area as well.

The vegetative seizures (respiratory and tachycardiac seizures sometimes accompanied by blood-pressure paroxysms) can be explained by the existence of a vegetative representation in the motor precentral cortex. This matter has been discussed in detail by Margareth Kennard (1949), Grinstein (1958) and Arseni and Samitca (1958). Our data confirm also the clinical and physiological researches of Poilici (1957) who studied a series of patients with vascular brain lesions or with supratentorial tumours, proving the importance of the right hemisphere for the control and functional adjustment of the vegetative respiratory and vasomotor centres. Before the analysis of the expressive amusia and dysphasia of our patient we should emphasize that up to July 1957, he never had any troubles concerning his ability to sing or play the accordion; the facio-brachial paresis and dysphasic troubles appeared, as we have shown,

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on the operation table, and a little later the patient became aware of his inability to sing or play.

The analysis of the musical dysfunctions in our patient shows that he had disturbances of the rhythmic sense and praxic disturbances.

(*a*) *Rhythmic dysfunction.*—As we have seen this dysfunction is attested by the fact that the patient lagged behind when singing with accompaniment, and by the lack of definite rhythm in spontaneous production.

Generally speaking, some of these disturbances seem to suggest the idea of a dysgnosic phenomenon (especially the inability to reproduce the given rhythms). We think, however, that rhythmic sense is a function of superior integration, the limits of which are considerably larger than the range of the musical functions.

Luria (1947) and Kreindler and Fradis (1957) studied the time sense and the rhythm test in aphasic patients. As the latter authors have shown, this test makes it possible "to establish exactly the balance and mobility of the excitation and inhibition processes within the motor analyser in normal and pathological conditions." This means that the correlation between excitation and inhibition which, as shown by Pavlov (1951), are the fundamental processes of higher nervous activity, is determinative for the quality of rhythm reproduction.

On the other hand it is possible that the described rhythm disturbance has also an apraxic origin. Indeed, this disturbance is evident in the "abstract rhythm" proofs (percussion with the hammer). The same rhythm is reproduced correctly if it is "bound" to a musical sound or integrated in a melody (facilitation phenomenon). There is some analogy between this phenomenon and another which has been described in some dysphasic patients, who can pronounce correctly and distinctly complicated words and sentences, as soon as they sing them. The major difficulty experienced by our patient is to abstract the rhythm, to dissociate it from the melodic element of music.

(*b*) *Musical dyspraxic phenomena* are undoubtedly predominant in the patient's clinical picture. Vocal spontaneous production and reproduction showed from the very beginning important intonational and rhythmic deficiencies. The agnosic component was wholly missing: indeed, the patient was conscious of and pointed out each fault of his own or of the examiner. Moreover, a careful examination of the tests proved clearly that he had no disturbances of the receptive type.

A most remarkable phenomenon was the transposition to the fourth involuntarily performed by the patient as he tried to reproduce separate sounds. This phenomenon appeared only when the patient had to reproduce separate sounds, and never occurred with a melody. It appears that in this case, too, one can speak of a loss of the ability to abstract sounds, as component elements, whilst the constructive scheme of the melody persists. As to the fact that the patient's reproduction is

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not simply a "false" one *but a systematic transposition to the superior or inferior fourth*, we think that our patient was affected by a special variety of apraxia which we should call *vocal transpositional* apraxia, as the characteristic element is the performed transposition. At present we have not sufficient knowledge to explain this surprising phenomenon; we can only draw attention to it, as an interesting semiologic feature.

The patient's attempts to reproduce vocally simple melodies were deficient, both intonationally and rhythmically. We should furthermore add the sometimes harsh, staccato and tremolo vocal emission. The inability to control the strength (amplitude) of the emitted sound made him unable to perform the requested dynamic variations, although these same variations were perceived correctly in the performance of another person. The same may be said about the agogical changes (tempo variations, accelerando, ritardando). Here, the difficulty experienced is still more important because of the associated rhythmic disturbance which has been described.

The intonational deficiencies in singing were more striking in the ascending passages of the melody. The difference in the quality of reproduction of ascending and descending scales has been observed also by Jellinek (1933). It is known from the pedagogical experience that children who are at the very beginning of their musical studies perform the descending scale more easily and sooner than the ascending one. It may be suggested that from the motor and praxic point of view the strain of the neuromuscular apparatus of phonation is increasing in the ascending scale, and decreasing in the descending one, the emission of the deepest sounds being the easiest.

The motor apraxia also made whistling difficult which the patient had practised vigorously before the operation.

However, the most evident praxic disturbance appeared when the patient tried to play on the accordion, an instrument he had played since the age of 9, using it before his illness to earn his living. Handling this familiar instrument, he was unable to play spontaneously or reproduce anything. If he tried to produce a melody by manipulating the keys with his right hand he was unable to use his left at the same time. If told to use his left, too, he played the harmony but at once stopped using his right hand. The extremely slight motor deficiency of the left hand could not be incriminated, because if this deficiency were responsible for the disturbance, why should it suddenly disappear when the patient ceased to play with his right? It may be rather suggested that this dissociation is due to a disintegration at a superior level of the complex praxic process which implicates the co-ordination of bimanual activity during the process of normal playing on the accordion (or any other polyphonic instrument). There is some analogy between this phenomenon and the case of a learner typist who can type normally with each of his hands

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apart, but is unable to use them simultaneously in the co-ordinate process of type-writing. Moreover, in the process of studying the manipulation of bimanual musical instruments the pupil learns first to play with each hand separately whilst simultaneous polyphonic playing is a later and higher degree of training. The exclusive *bimanual instrumental* apraxia presented by our patient reminds us of this elementary degree of instruction.

However, the process of praxic disintegration seems to go still farther. Knowing that in his past the patient used frequently to sing, accompanying himself at the same time on the accordion, we asked him to try such a performance. As we have seen, whilst there was a relatively good vocal production (better than the unaccompanied one), the "accompaniment" was a real chaos which had not the least harmonic or tonal relation with the vocal part. The deep degree of dissociation between the vocal and instrumental parts was proved by the surprising fact that this *sui generis* accompaniment did not induce the slightest tonal deviation or mistuning of the vocal part. The praxic system of phonation appeared also as totally dissociated from the instrumental one, the two productions having a wholly independent development.

Analysis of the expressive dysphasia.—The language disturbance was mainly an expressive speech defect with tachyphemy. The ability to pronounce normally separate words contrasted with the expressive deficiency which appeared during the utterance of long phrases. Immediately after having been operated upon the patient experienced a difficulty in finding less common words and an occasional difficulty in comprehension of complicated requests. A year later he presented only a slight articulation difficulty. The appearance of dysphasia and dysmusia in a right-handed man following a lesion in the right frontal lobe leads us to the controversial problem of cerebral dominance in relation to preferred hand (handedness).

We do not intend to discuss in detail the aspects of crossed aphasia (Bramwell, 1899). The problems of cerebral dominance and crossed aphasia have been studied by a large number of authors who published a series of valuable papers on this matter (Head, 1923; Brain, 1941; Girard, 1952; Humphrey and Zangwill, 1952; Goodglass and Quadfasel, 1954; Zangwill, 1954; Critchley, 1957, and others).

Ettlinger, Jackson and Zangwill (1955) discuss the 16 clinical reports published till now in which aphasia has been found in association with right-sided lesions in right-handed patients.

Discussing the problem of crossed aphasia in right-handed people, Hécaen and Ajuriaguerra (1956) express the opinion that "Les cas d'aphasie croisée chez les droitiers semblent avoir été surestimés."

Foster Kennedy (1916) suggested that the appearance of aphasia in a right-handed person with involvement of the right hemisphere should

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be connected with a familial predisposition proved by the existence of a familial left-handedness. The problem has been discussed also by other authors and recent studies confirm the existence of a connection between these two facts.

Indeed there are only two authentic cases (Mendel, 1914; Marinescu, Grigorescu and Axente, 1932, 1938) in which neither personal nor familial indications of left-handedness could be established. Our patient's elder brother was left-handed, left-footed and right-eyed which proves that in our case there was also a tendency to familial left-handedness.

The presence of dysprosody is interesting from the semiological point of view and also in connexion with the fact that the right-handed patient of Ettlinger, Jackson and Zangwill (1955) had the same disturbance. This patient presented a receptive dysphasia following a right temporal lobectomy.

As to localization, the lesion, in our case, involved the posterior part of the right first two frontal convolutions. Anatomical data are in accord that there is an instrumental motor centre at the foot of the second frontal convolution in the dominant hemisphere (Henschen, 1925). Although it is difficult to estimate the extent of the lesion, it is possible that the pars triangularis of the third frontal convolution was also involved in the operation, as we know that the tumour invaded also the subcortical portion of this area. This region (left-sided in right-handed people) is considered by most of the authors (Henschen, 1925, 1926; Nielsen, 1946) the centre for vocal singing. Our report stresses once more the problem of the connexion between the so-called minor hemisphere and the musical functions (Henschen, 1925; Feuchtwanger, 1930).

To establish the cerebral laterality for language in our patient one must consider the following facts:

(*a*) The expressive dysphasia was slight from the beginning and improved quicker than the musical troubles. It is known that in the majority of operated cases with space-occupying lesions, the brain-cortex shows a great compensatory capacity (Behtereva, 1954; Kovalev, 1958). Clinical data (Botez, 1958) show that in the period immediately following operation in similar cases, aphasia is much more severe than it was in our case (one has to consider besides the tumour, the œdema and distant vascular troubles). Slight speech-disturbances at the beginning and their rapid compensation support the hypothesis of a bilateral representation of speech in our patient's brain.

(*b*) We know that right cerebral laterality for language is much less prevalent than left-handedness, and left cerebral laterality for language is more prevalent than right-handedness (Goodglass and Quadfasel, 1954). Moreover, Roberts (1951), studying a series of patients operated

upon by Penfield, reports that aphasia followed operations on the right hemisphere only twice in 258 right-handed patients and three times in 23 left-handed patients (cortical excisions for the relief of focal epilepsy).

(*c*) The presence of a specialized dyspraxia is also a criterion of cerebral dominance (Ettlinger, Jackson and Zangwill, 1956). In our case, this dyspraxia was evident in connection with the musical production (vocal and instrumental).

Considering all the facts, we think that our congenitally right-handed patient had a bilateral representation of expressive and receptive language, and a unilateral representation (in the right hemisphere) of expressive musical functions. It can be suggested that a familial tendency to left-handedness is connected up to a certain point with this dissociation of the brain functions.

SUMMARY

The case is reported of a right-handed patient who had an oligodendroglioma in the posterior third of the first two frontal convolutions of the right cerebral hemisphere. After the operation the patient exhibited transitory expressive dysphasia with dysprosody and a lasting expressive dysmusia, the characteristics of which are described.

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PLATE XXI

FIG. 1.

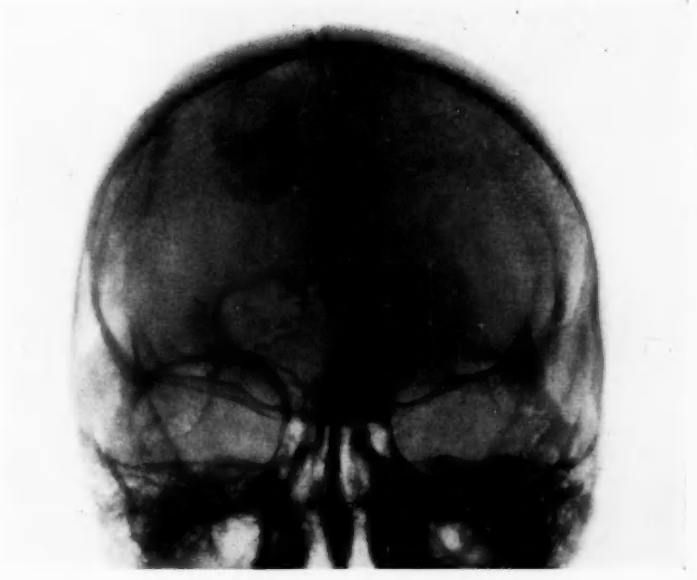

FIG. 2.

To illustrate article by M. I. Botez and N. Wertheim.

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AN INHERITED DISEASE SIMILAR TO AMYOTROPHIC LATERAL SCLEROSIS WITH A PATTERN OF POSTERIOR COLUMN INVOLVEMENT. AN INTERMEDIATE FORM?

BY

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INTRODUCTION

INHERITED neurological disorders are assumed to be due to genetically determined abnormalities which affect the neurones. The nature of the abnormality in most instances is not known, but may be referred to in the general sense as "metabolic." At the cellular level, the abnormality may be related to (*a*) improperly constituted neurones, which might function relatively well for a period of time before deteriorating, (*b*) the lack of a nutritive factor essential to neurones which other cells fail to make available, or (*c*) a detrimental substance which other cells add to or allow to enter the neuronal environment. The clinical and pathological manifestations of a given abnormality are modified by exogenous and genetically determined endogenous factors. Since genetic modifying factors are assumed to be more nearly similar in members of the same family, intrafamilial variations in the manifestations of a given abnormality are expected to be less than interfamilial variations.

In the classification of inherited neurological conditions, certain variations of a disease entity are accepted in order to avoid calling each clinical and pathological variant a new disease. Hence, proper classification depends upon the ability to distinguish between (*a*) variations in the manifestations of the same abnormality and (*b*) similar clinical and pathological manifestations of different abnormalities. Only variations in the manifestation of the same abnormality may properly be considered as being closely related members of a continuum.

A close relationship between two distinct disease entities is sometimes inferred from the appearance of each in its usual form in members of one family or from the existence of an "intermediate" or "linking" form with features of both disease entities in one person. Possible relationships between a number of inherited neurological disorders have been considered. A few examples may be cited. Roth (1948), Greenfield (1954),

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and Schut (1954) reviewed the interrelationship between forms of spinocerebellar ataxia. These authors also considered the relationship of peroneal muscular atrophy, familial spastic paraplegia, hereditary optic atrophy, hypertrophic neuropathy, and some myopathies to the hereditary ataxia group. Aring and Cobb (1935, 1954) stated that a "group of neural myopathies should be looked upon as one disease with many variants" (1954), the variants being infantile spinal muscular atrophy, familial spastic paraplegia, hypertrophic neuropathy, peroneal muscular atrophy, familial arreflexia, familial ataxia with optic atrophy, cerebellar ataxia with or without optic atrophy, and hereditary optic atrophy. Neurofibromatosis has been associated with tuberous sclerosis (Urbach, Wiedmann, 1929), and with hypertrophic neuropathy (Bielshowsky, 1922). Austin (1958) discussed the relationship of recurrent polyneuropathy to neurofibromatosis, hypertrophic neuropathy, acute ascending paralysis, and acute facial palsy. Stucki and Luban (1953) discussed the relationships between peroneal muscular atrophy, Friedreich's ataxia, hypertrophic neuropathy, progressive muscular atrophy, spinal muscular atrophy, and neurofibromatosis. Progressive muscular atrophy, amyotrophic lateral sclerosis, and progressive bulbar palsy are considered closely related (Wilson, (1955) and are therefore termed forms of "motor neurone disease." Motor neurone disease has been related to infantile spinal muscular atrophy (Davison, 1952), cortico-striato-spinal atrophy (Meyer, 1929), circumscribed cortical atrophy (Kloepfer, 1956), paralysis agitans (van Bogaert and Radermecker, 1954), and familial periodic paralysis (Biemond and Daniels, 1934).

In this report, two families manifesting what may be an intermediate form of neurological disorder will be presented. The condition observed was clinically indistinguishable from amyotrophic lateral sclerosis (ALS). In the first family there were at least 11 affected persons in four generations; in the second family there were 3 affected persons in two generations. Pathological examination of one case in the first family and of two cases in the second family revealed, in addition to severe involvement of the lower and upper motor neurones, an unexpected pattern of posterior column demyelination. Greenfield (1958), after having seen our material, suggested that "these cases link ALS to cases of familial spinocerebellar degeneration with amyotrophy (Schut and Haymaker, 1951)." Because there are similarities between our cases and other neurological disorders in addition to ALS, the possibility that these cases represent a link in a broad continuum of inherited neurological disorders will be considered.

Case Reports

Family A

The first family (fig. 1) is "Pennsylvania Dutch" and has resided in north-central Pennsylvania for at least a hundred years. The illness is

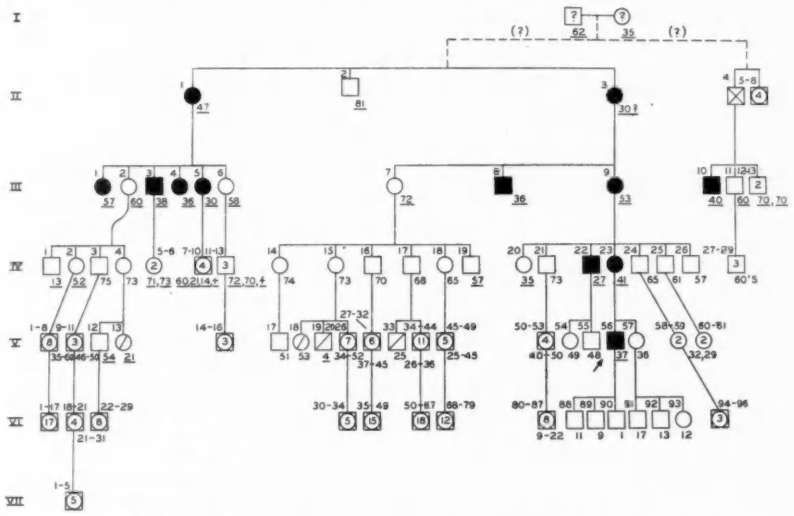

FIG. 1.—Inheritance pattern of "Pecks' Disease" in Family A.

referred to as "The Family Disease" or "Pecks' Disease" (the earliest ancestors known to have been affected, II-1 and II-3, were Pecks). All members of the family but one (V-18) were of normal intelligence. Persons other than those mentioned below were free of neurologic disease. No consanguineous marriages were reported. Nearly all of the living descendants of III-9, most of the children of III-7 and many of their descendants, and IV-3 were personally examined. There was no family history of miscarriages, anæmia, blindness, foot or finger deformities, hydrocephaly, hearing defects, or other congenital abnormalities. However, it was stated that members of the family who did not die of "The Family Disease" frequently had chronic lung disease which was said not to be tuberculosis. One autopsy was obtained in this family.

Case report.—V-56, E. M., Propositus. He was a married white male foreman in a camera manufacturing company. In January 1956, at age 36 years, following a period of unusual physical exertion and fatigue, he first noted inability to extend his left middle finger. The weakness slowly increased and gradually spread to involve other fingers of the left hand. During the next month he noted a "knotted" feeling in the left calf and thigh associated with the onset of progressive weakness in the left lower extremity. There were many muscular twitchings in the left forearm, arm, chest, thigh and leg.

In July 1956 neurologic examination revealed an intelligent and co-operative patient with muscular weakness and atrophy distally in the left upper extremity and proximally in the left lower extremity, with normal strength on the right side. There were numerous fasciculations in the skeletal muscles on the left. The muscle stretch reflexes were decreased on the left, normal in the right upper extremity, and increased in the right lower extremity. Abdominal reflexes and plantar responses were normal,

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as were the cranial nerves, co-ordination, and sensation of all modalities. Laboratory studies, including urinalysis, white blood cell count and differential, hæmoglobin and hematocrit, sedimentation rate, serologic test for syphilis (blood), blood urea nitrogen, and fasting blood sugar, were normal. Biopsy of the left vastus lateralis muscle showed a severe neurogenic muscular atrophy.

The wasting and weakness rapidly progressed, so that by November 1956 there was a left flaccid atrophic hemiplegia with only slight toe movement possible on that side. The left extremities were cold and blue distally. The musculature on the right side was only slightly affected. The patient could walk with the aid of a cane. His face appeared wasted bilaterally, his voice was hoarse, and his sternomastoids were weak bilaterally. All muscle stretch reflexes were absent in the left extremities and normal or slightly decreased on the right side. Plantar responses were flexor, palmomental reflexes were absent, and the abdominal reflexes, jaw-jerk, co-ordination, and sensation were normal. The tip and lateral borders of the tongue were reddened compared to the appearance five months previously. Repetition of earlier laboratory studies again showed normal values. In addition, there was free HCl in the fasting gastric juice. Calcium, phosphorus, magnesium, alkaline phosphatase, total protein, and the albumin: globulin ratio in the serum were normal. Cytologic examination of gastric tissue obtained by aspiration after trypsinization showed no abnormalities.

During the last four months of his illness, the patient complained of belching, abdominal pain, and diarrhœa after eating cucumbers, radishes, or tomatoes. There had been no previous intolerance to these foods. Muscle weakness progressed to involve the right extremities and prevent walking. Respiration became difficult and in January 1957, twelve months after the illness began, the patient died during an exacerbation of chronic bronchitis complicated by bronchopneumonia and atelectasis.

The patient had received 1,000 mcg. of vitamin B_{12} intramuscularly twice weekly from June 1956 until four months prior to death, after which time the same dose was given daily until death. Other ineffectual medications were potassium iodide, multivitamins, and brewer's yeast.

General autopsy findings.—The examination showed passive congestion of the kidneys, spleen, and liver. The lungs contained scattered foci of bronchopneumonia and small granulomatous lesions of Boeck's sarcoid. In the cardia of the stomach there were slight chronic inflammatory changes. The wasted skeletal muscles showed neurogenic atrophy. Other findings included old fibrous pericarditis, a small cutaneous hemangioma on the right ear, and bilateral pingueculæ.

Central nervous system findings.—The spinal cord and brain showed no abnormalities on gross examination. The formalin-fixed brain weighed 1,483 grammes.

Spinal cord.—Microscopic examination of various levels revealed changes within both grey and white matter. In the lumbar segments, there was conspicuous degeneration of the anterior horn motor neurones, particularly in the dorsolateral group. There was central chromatolysis with peripheral displacement of the nucleus in many of these cells. Some of the neurones were completely devoid of Nissl substance and some contained an increased amount of lipofuscin. Others were pale, shrunken, and recognizable only by their general outline. Occasionally, degenerated nerve cells were observed in the posterior horns. In a few instances, a cluster of microglia cells surrounded remnants of a nerve cell. The anterior horns appeared very cellular due to intense astroglial and microglial proliferation. The myelin preparations revealed diffuse pallor of the myelin in the anterior and the lateral columns, which was most marked at the periphery of the spinal cord. In the posterior columns there was well-defined myelin loss in the intermediate portion (fig. 3). Astroglial proliferation within the white matter was associated with the loss of myelin. Microglial rosettes were occasionally found scattered in the white matter. The anterior roots appeared atrophic and showed poor preservation of the myelin.

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In the thoracic segments, degeneration of the anterior horn neurones was pronounced, and only a few cells of normal appearance were recognized. Some of the neurones in Clarke's columns appeared pale and shrunken. The loss of myelin in the thoracic levels was similar in distribution and intensity to that of the lumbar levels. Sections counterstained with Sudan IV revealed neutral fat in the lateral corticospinal tracts.

In the region of the cervical enlargement, the few remaining anterior horn neurones showed various pictures of degeneration (central chromatolysis, shrinkage, hyperchromasia). Astroglial and microglial reaction was very intense and numerous glial clusters were noted. The myelin preparations showed peripheral loss of myelin in the anterior and lateral columns, where the dorsal and ventral spinocerebellar tracts were particularly affected. Involvement of the lateral corticospinal tracts could be ascertained only in sections counterstained for neutral fat. The posterior columns showed myelin pallor in the anterior two-thirds of the fasciculi cuneati with sparing of the posterior one-third and of the fasciculi gracili.

In the upper cervical segments, in addition to the diffuse myelin pallor of the anterior and lateral columns, there was a conspicuous myelin loss in the dorsal spinocerebellar tracts; the ventral spinocerebellar tracts were less severely involved. The myelin loss in the posterior columns was moderate in an oval area of the medial and anterior three-fourths of the fasciculi cuneati and slight in the medial paraseptal areas. Otherwise, changes in the neurones and glia were similar to those of the lower cervical regions.

In all of the spinal cord sections examined, occasional vessels showed scant perivascular lymphocytic infiltrations. Amyloid bodies were numerous, particularly at the periphery of the spinal cord. Intense proliferation of the ependymal cells around the central canal was observed in all sections studied. Neutral fat was present in all areas showing loss of myelin.

Medulla and pons.—The XII nerve nuclei showed definite reduction in the number of neurones. Some of the remaining neurones appeared to be well preserved, while others showed chromatolysis or shrinkage. The dorsal motor nuclei of X contained occasional cells with distended cytoplasm and no recognizable Nissl substance. The motor nuclei of V contained numerous pale, shrunken, or darkly stained neurones. Slight neuronal changes were evident in the ambigual and facial nuclei. Myelin pallor was recognizable in both spinocerebellar tracts in the medulla. The corticospinal tracts were diffusely pale in comparison to the darkly stained medial lemnisci. In the pons, the corticospinal tracts appeared normal. Astroglial and microglial proliferation was moderate in the region of nuclei with neuronal degeneration and in white matter showing myelin loss. Holtzer preparations demonstrated dense glial fibrosis in the region of the inferior olives and the lateral cuneate nuclei which appeared possibly greater than normal for these areas. There was slight lymphocytic infiltration in the perivascular spaces of a few small vessels in the medulla and pons.

Mid-brain.—A few vessels showed slight perivascular lymphocytic infiltration. Several microglial rosettes were present in the corticospinal tract areas of the peduncles.

Basal ganglia, thalamus, and cerebellum.—Nothing abnormal was noted.

Cerebral cortex.—The changes were most pronounced in the motor cortex. Neurones of the third and fifth layers were frequently shrunken and hyperchromatic or showed loss of Nissl substance. Betz cells appeared to be reduced in number and occasionally showed microglial neuronophagia (fig. 6). There was a noticeable astrocytic proliferation, particularly in the third and deeper cortical layers and in the underlying white matter. The other cortical areas showed less conspicuous changes which were limited to occasional neuronal degeneration and moderate, diffuse astrocytic proliferation. The vessels throughout the cerebral cortex and the subcortical white matter frequently showed fibrous adventitial thickening and a few lymphocytes and glitter cells were observed in the perivascular spaces.

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Other affected members.—IV-23, R. S. M., mother of the propositus. One month following an operation for goitre, she noted weakness in her left index finger and back which gradually spread to involve the left hand, arm, and foot. The upper limbs were weaker than the lower limbs. She became confined to bed, had difficulty breathing, and died at age 41 years after an illness of less than one year's duration.

IV-22, W. S., maternal uncle of the propositus. Weakness on the left side started in association with intermittent aching in the legs and was followed by muscular twitchings and "loss of flesh." He died in his sleep, at age 27 years, after an illness of eighteen months. He is said to have walked with a limp to the county fair the day before he died.

III-9, F. A. S., maternal grandmother of the propositus. "Creeping Paralysis" began near her left knee and forefinger and progressed to affect the left side predominantly. She was confined to a chair and then to bed for six months prior to death. She died at age 53 years, one and a half to two years after the onset of her illness.

III-8, H. A., brother of III-9. He died of pneumonia, at about 36 years of age, after having had "Creeping Paralysis" for one to two years. In the last few months before death he was so weak that he could not get out of a chair and could not walk.

II-3, E. Peck A., maternal greatgrandmother of the propositus. She died at about 30 years of age of "Pecks' disease." It started in her heel, spread quickly over the body and "hit the heart."

II-1, J. Peck G., sister of II-3. She died at age 47 years of "Pecks' disease."

III-1, E. G., daughter of II-1. At age 56 years, weakness started in her left thumb, moved up her left arm, affected the left side of her body, and then crossed over to the right side. "It took the flesh off." Although she could not walk, she was not confined to bed prior to her death, which occurred six months after the onset of her illness.

III-3, B. G., son of II-1. At age 37 years, muscle weakness started in his left hip. He was able to work throughout one winter but died the following March, the illness having lasted less than one year. Near the end of his life he tied a rope around his left foot to help lift it when walking.

III-4, H. G., daughter of II-1. She died ("choked to death") of "Pecks' disease" at age 36 years.

III-5, F. G. S., daughter of II-1. She died at 30 years of age of "Pecks' disease," after having been confined to bed by weakness.

Suspected members of the family.—III-10, E. Peck. No definite relation to this family was found, but he lived in the same county. He is said to have had "Pecks' disease" manifested by "just weakness and loss of flesh," initially about the right knee and later spreading to the left side. He died at age 40 years.

II-4, J. Peck, father of III-10. No definite information was obtained, but a descendant (IV-27) said he died of "Pecks' disease."

I-1, C. Peck, definite relationship to the family is uncertain, but he could be a common ancestor as shown on the diagram. He died at age 62 years, cause unknown.

II-2, E. Peck, wife of I-1. She died about age 35, cause not known.

Members of the family with other neurologic conditions.—V-33, C. G. At 18 years of age, he had an acute ascending paralysis from which he subsequently made a complete recovery. When examined seven years later, there was no evidence of neurologic disease.

V-18. E. W. She is 53 years old, an imbecile since birth, but without motor system involvement.

V-19. L. W. He died at age 4 years of "infantile paralysis followed by pneumonia."

V-13. F. S. At age 21 years, after an illness lasting one month, she was "out of her head" for three days, became comatose, and died.

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Family B

All members of this family (fig. 2) were born and raised in Louisiana and were of normal intelligence. No consanguinity was reported. Autopsy studies of two persons dying of the familial disease were available. Living members of the pedigree not specifically mentioned are in good health.

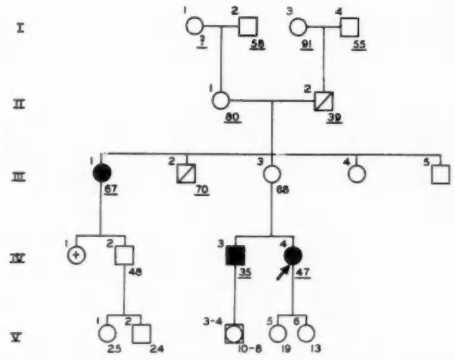

FIG. 2A.—Inheritance pattern in Family B.

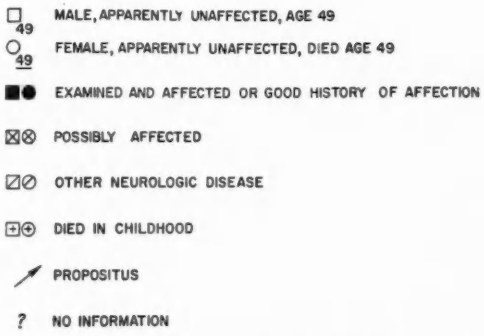

FIG. 2B.—Key to inheritance pattern charts.

Case Report.—IV-4, E. M., propositus. She was a married white female housewife whose illness began insidiously with weakness in the lower extremities in January 1955, at age 46 years. Her illness progressed steadily. By June 1955 her upper extremities were also affected, particularly on the right side. Muscle "soreness" and "paræsthesias" were recorded by one observer, without further clarification. Muscle stretch reflexes were equal and active in the upper extremities; the knee and ankle jerks were absent on the right and present on the left. Plantar responses were normal and no objective sensory loss was found. Laboratory studies disclosed no abnormalities in the red cell

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and white cell counts, sedimentation rate, gastric acidity, and blood serologic test for syphilis. Electromyography showed denervation and a few fasciculations in both legs and the right arm.

The progression of weakness and wasting continued. By May 1956 respiratory distress necessitated the use of a respirator at night. The patient had complete flaccid atrophic weakness of the right lower extremity and severe flaccid atrophic weakness of the other extremities. Facial weakness and slight weakness of the muscles of mastication were present on the right. The right side of tongue was weak but atrophy was not evident. The left plantar response was equivocal and Hoffmann's sign was present on that side. Death due to respiratory failure occurred twenty months after onset of her illness.

General autopsy findings.—In addition to foci of bronchopneumonia, the lungs showed moderate generalized fibrous hyperplasia. Several old healed tubercles were found in the spleen and in the hilar lymph nodes of the lungs. The left ventricle of the heart contained a small healed myocardial infarct. There was a benign submucous polyp in the uterine cervix. Sections of several skeletal muscles showed neurogenic atrophy.

Central nervous system findings.—The spinal cord and brain revealed nothing abnormal on gross examination.

Spinal cord.—Microscopic examination of sections taken at various levels revealed marked neuronal degeneration in the anterior horns and loss of myelin in several areas of the white matter. Anterior horn neurones were reduced in number; the remaining ones frequently showed central chromatolysis, hyperchromatosis, or shrinkage. In Clarke's columns only a few pale or shrunken neurones were recognized. The pattern of myelin degeneration (fig. 4) resembled that of V-56 in Family A described above. In the lumbar segments, there was diffuse pallor of the myelin in the anterior and lateral columns and well-defined demyelination in the middle third of the posterior columns. At thoracic levels, the anterior and lateral columns were diffusely pale with accentuated pallor in the ventral spinocerebellar tracts. In the posterior columns there was circumscribed pallor in the middle third of the fasciculi cuneati and slight involvement of the medial paraseptal areas. At cervical levels, pallor of the anterior and lateral columns was also present. The spinocerebellar tracts showed a moderate loss of myelin but there was a conspicuous sparing of the most peripheral zones at the attachment of the dentate ligaments. The spared regions could represent fibres which do not

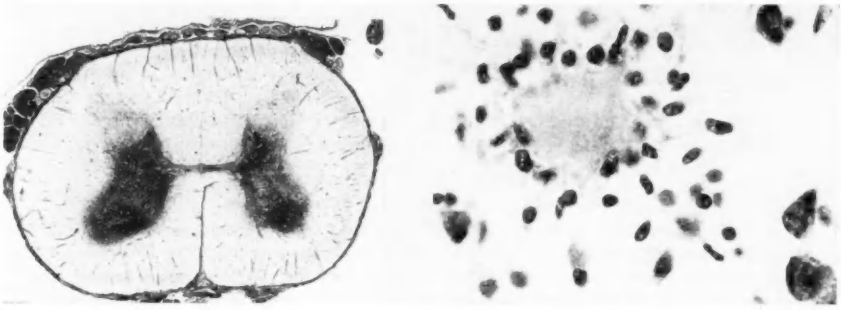

FIG. 5.—Section of the spinal cord at the lumbar level from B, IV-4. Holtzer stain for glia.

FIG. 6.—Neuronophagia of a Betz cell in A, V-56. Cresyl violet stain.

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belong to the spinocerebellar system (J. G. Greenfield, personal communication). The posterior columns showed myelin pallor in an oval medial portion of the anterior three-quarters of the cuneate fasciculi and of the medial paraseptal areas. Astroglial and microglial proliferation was intense in the anterior horns thoughout the various levels (fig. 5). There was diffuse gliosis of the white matter, accentuated in the spinocerebellar tracts and in the areas of the posterior columns which showed myelin loss. In the latter areas large gemistocytic astrocytes were prominent.

Medulla and pons.—Neuronal degeneration was present in the nuclei of XII and the motor nuclei of V. Neurones of these nuclei frequently showed swelling, loss of Nissl substance, or shrinkage and hyperchromatosis. A few microglial clusters were observed. Pallor of the myelin was evident in the ventral and dorsal spinocerebellar tracts. In the corticospinal tracts, no loss of myelin was noted.

Mid-brain, basal ganglia, thalamus, and cerebellum.—Nothing abnormal was observed.

Cerebral cortex.—The changes were confined to the motor cortex. There was appreciable astrocytic gliosis and increase in the number of perineuronal satellites. Microglial neuronophagia of Betz cells was occasionally observed.

Other affected members.—IV-3, R. F., brother of the propositus. He was a married white male aeronautical engineer whose illness began with progressive weakness of the right arm and shoulder in January 1948, at age 35 years. The weakness spread to involve the forearm and hand muscles so that within four months he had a complete flaccid paralysis of his right upper extremity. The left lower extremity next became weak, first proximally and later throughout the entire limb. Paresis developed in the left upper limb. In April 1948 he noted the onset of small generalized twitchings of the muscles. The treatment he received included multivitamins, tocopherol, prostigmine, pyridoxine, thyroid extract (BMR's had been −32 and −30), and physiotherapy.

By July 1948 he was totally incapacitated with flaccid atrophic paresis of both upper extremities and the left lower limb, while the right lower limb had normal power. There was only barely perceptible flexion of the left hand, left foot, and right index finger. The right knee-jerk was brisk, the right ankle and left biceps-jerks were sluggish, and all other tendon reflexes were absent. There were no definite signs of upper motor neurone involvement. Sensation and intellect were normal. Laboratory studies showed no abnormalities in the hæmoglobin, white blood cell count, blood Wassermann reaction, serum cholesterol, serum protein, and albumin : globulin ratio. The cerebrospinal fluid examination disclosed 65 mg. per cent protein, no cells, and a negative Wassermann reaction. X-rays revealed a large amount of gas in a dilated stomach which elevated the left diaphragm leaf.

The weakness continued to progress. In October 1948, nine and a half months after the onset of his illness, the patient had an episode of sudden dyspnœa with sweating, said he was in no distress, but then suddenly ceased breathing.

General autopsy findings.—There was diffuse severe neurogenic muscular atrophy. The lungs showed atelectasis, œdema, and some patchy bronchopneumonia. There was a small, encapsulated adrenal cortical adenoma. The thymus was moderately enlarged. There was partial fusion and calcification of the aortic valve cusps.

Central nervous system findings.—The brain weighed 1,200 grammes and appeared grossly normal. Sections of the spinal cord revealed hyperæmia of the anterior horns. Only the spinal cord and the tegmental portion of the pons were available for microscopic study.

Spinal cord.—Microscopic study revealed pronounced degenerative changes in the anterior horn neurones in all segments studied. Some of the neurones were swollen and devoid of Nissl substance; others were shrunken or hyperchromic. There was a

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conspicuous reduction in number of the anterior horn neurones. Astroglial proliferation was marked in the anterior horns and moderate throughout the white matter. Several microglial rosettes were seen in the lateral columns. Myelin loss resembled that of A, V-56 and B, IV-4. At the lumbar levels, loss of myelin was most severe in the posterior columns, where it was nearly complete except for some sparing of the anterior and posterior portions. The lateral and anterior columns showed slight diffuse demyelination, especially in the peripheral zones and in one lateral corticospinal tract. At the thoracic levels, there was slight diffuse myelin pallor of the posterior columns. The lateral and anterior columns showed myelin pallor in the entire peripheral zone and in both lateral corticospinal tracts. At the cervical levels, there was moderately severe loss of myelin in the posterior columns involving the anterior three-quarters of the fasciculi cuneati and the posterior medial paraseptal areas. There was sparing of in-between areas and of the posterior quarter of both the gracili and cuneati fasciculi. The lateral and anterior columns showed diffuse myelin pallor.

Tegmental portion of the pons.—Nothing abnormal was noted.

III-1, R. B., maternal aunt of the propositus. She was a married white housewife who noted the onset of painless weakness in the left lower limb in October 1949, at age 65 years. In November 1949 examination revealed muscular weakness and atrophy of the left thigh and leg. The left ankle-jerk was absent. There was no sensory loss. In March 1950 spinal fluid examination was normal.

The flaccid atrophic weakness progressed to involve the entire left lower extremity. The right lower extremity was next affected, and soon afterward the upper limbs were affected. Respiration became difficult and death occurred two and a half years after onset of the illness. An autopsy was not performed.

Other members.—III-2, E. V., maternal uncle of the propositus. He died at age 70 years, in October 1956. Autopsy revealed: meningovascular and aortic syphilis; chronic pylonephritis, renal calculi, and uræmia; terminal bronchopneumonia; a small hamartoma of the gall-bladder; and an adrenal cortical adenoma, 8 mm. diameter.

II-2, maternal grandfather of the propositus. He is said to have had "locomotor ataxia" and to have died at age 39 years of a "stroke."

III-3, mother of the propositus. In September 1958 she reported that she was well and had no symptoms of neurologic disease. At that time she was 68 years of age.

II-1, maternal grandmother of the propositus. She died of pneumonia at 80 years of age. There was no evidence of neurologic disease.

I-1. No information.

I-2. He died at age 58 years of cancer.

I-3. She died at age 91 years, cause unknown.

I-4. He died at age 55 years of cancer.

III-4, 5. No information is available but they are thought to be alive and well.

Discussion

A. *Similarities of the Reported Cases to ALS*

Since the original descriptions (Duchenne, 1849; Aran, 1850; Charcot and Joffroy, 1869), there have been numerous reports of ALS and its variations. The conditions *usually*: (*a*) begins in adult life (30–65); (*b*) is subacute in duration, terminating fatally within one to four years; (*c*) clinically manifests only upper and lower motor neurone signs without sensory, extrapyramidal, sphincter, or mental changes; (*d*) pathologically shows severe involvement of the spinal cord, without posterior column changes, which diminishes on ascending to brain stem and higher levels; (*e*) is not hereditary.

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In the cases presented, the age of onset (25–65, median 36), duration of illness (six months to two and a half years, median one year), and clinical manifestations (severe lower motor neurone signs with some evidence of upper motor neurone involvement) were compatible with ALS. The asymmetric involvement present in some of the cases is not uncommon in the early stages of ALS. Neither sensory loss, mental change, extrapyramidal involvement, nor loss of sphincter control was demonstrated in any of the four clinically well-studied cases. The majority of the neuropathological findings were compatible with ALS. These included: degeneration of motor neurones, severe at spinal levels, moderate at brainstem and cortical levels; demyelination of the corticospinal tracts and of more diffuse areas in the lateral and anterior columns of the spinal cord; gliosis in areas of demyelination and neuronal degeneration; slight lymphocytic cuffing of blood vessels in the cord and brain; and presence of amyloid bodies.

B. *Features of These Cases Uncommonly Noted in ALS*

(1) *Hereditary pattern.*—A hereditary form of ALS with a genetic pattern of dominant inheritance occurs infrequently but has been observed in the Chamorro population of the Mariana Islands and in numerous families of at least twelve other nationalities (Kurland and Mulder, 1954, 1955; Kurland, 1956). In Family A, "Pecks' Disease" behaved as an autosomal dominant trait apparently with complete penetrance, i.e. each affected person in the recent generations had an affected parent. Among sibships in which one or more persons were affected and among offspring of affected persons, 22 reached 50 years of age. Of the 22, 11 (7 of 13 females and 4 of 9 males) were affected. In Family B, the inheritance pattern was consistent with either a dominant trait showing incomplete penetrance or a recessive trait. The small number of affected individuals precludes a definite decision. If III-3 (a 68-year-old woman) becomes affected, the pattern will be compatible with a dominant trait showing complete penetrance. Sex-linkage was not present.

(2) *Posterior column involvement.*—In ALS, the posterior columns usually escape completely, but some cases have a slight pallor of the fasciculi graciles which "may be no greater than is sometimes seen in clinically normal subjects of similar age" (Greenfield, 1958). Degeneration of the fasiculi graciles in non-hereditary cases reported as ALS has been noted by Davison and Wechsler (1936), Lawyer and Netsky (1953), and Colmant (1958) (see his references). Diffuse or indefinitely localized demyelination of the posterior columns was shown in non-hereditary cases by Hassin (1933), Biemond (1941), Marks (1949) and Brain (1951).

Hasaerts-Van Geerthruyden (1955) reported a case of ALS with dominant inheritance in which the fasciculi graciles were demyelinated. A few of the hereditary cases of ALS from the Mariana Islands and from the United

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States showed slight generalized involvement of the posterior columns.

In all 3 of our autopsied cases, there was demyelination of the posterior columns in a particular pattern. This pattern of demyelination did not fit the boundaries of any tracts or "system." It did, however, closely resemble the pattern of fœtal myelination, in that the earliest myelinated fibres were the most severely demyelinated.

The stages of fœtal myelination of the posterior columns were well described by Flechsig (1876) and Trepinski (1898). They denoted zones whose location varies somewhat at different levels of the cord (fig. 7). The

FIG. 7.—Figures from Trepinski (1898) showing the pattern of myelination of the posterior columns at the seventh fetal month: A, lumbar, and B cervical levels.

heavily myelinated intermediate portion of the dorsal column in the lumbar area was called the "*middle root zone*"; this zone lies in the fasciculus cuneatus at cervical levels. The middle root zones are supposedly concerned with proprioception (Greenfield, 1958), but in spite of moderate to severe involvement of them and of the spinocerebellar tracts in our cases, no impairment of proprioception was detected clinically.

Pathological study of two cases of hereditary ALS other than those reported herein has disclosed a similar pattern of posterior column demyelination. It was of minimal degree in one American case reported by Kurland and Mulder (1954). In another American family presently being studied by Gardner and Garvey (1958), in which at least 16 of over 300 surveyed members in seven generations had ALS, the propositus demonstrated a very similar pattern of moderately severe posterior column involvement, especially at cervical levels (i.e. in the cuneate fasciculi).

Occasional non-hereditary cases reported as ALS (Pal, 1898; Mott and

Tredgold, 1902; Catola, 1925; Wimmer and Neel, 1928; Dagnélie and Cambier, 1933; Davison and Wechsler, 1936) have shown a similar pattern of demyelination in the posterior columns, although some of the earlier ones were not adequately distinguished from syphilis and vitamin B_{12} deficiency. We have recently observed a case with a negative family history which was clinically and pathologically similar to the cases presented in this report. The posterior columns showed middle root zone involvement predominantly at the cervical level.

A pattern of posterior column demyelination similar to that of fœtal myelination has frequently been demonstrated in Friedreich's ataxia, subacute combined degeneration of the cord (of the type associated with vitamin B_{12} deficiency), and tabes dorsalis. A similar pattern was also shown in ergot poisoning (Tuczek, 1882); in carcinomatous myelopathy (Greenfield, 1934; Zülch, 1936; Henson *et al.*, 1954); in a familial central nervous system degeneration of three siblings all dying by age 2 years (Lubin *et al.*, 1943); and perhaps in 2 cases (one having Hodgkin's disease) with the pathological syndrome of subacute combined degeneration of the cord without vitamin B_{12} deficiency (Zeman and DeLand, 1957).

C. *Relationship of These Cases to Other Inherited Neurologic Diseases*

(1) *Idiopathic spinocerebellar degenerations.*—The idiopathic spinocerebellar degenerations form a heterogeneous group. Most begin in childhood, have a prolonged course, and are inherited as recessive traits; some (Akelaitis, 1938; Greenfield, 1958) first appear in adult life, have a subacute course, and may show dominant inheritance. Pathological examination reveals degeneration mainly in the cerebellum, its afferent and efferent pathways, and the long motor tracts of the spinal cord, but not confined to these structures. The posterior columns sometimes show demyelination in a pattern like that of fœtal myelination. Anterior horn neurone involvement is uncommon but may occur. In our cases, the hereditary pattern and pathological involvement of the posterior and lateral columns resembled that occurring in some of the spinocerebellar degenerations. The severe clinical and pathological involvement of lower motor neurones which occurred in our cases is not found in the spinocerebellar degenerations.

(2) *Familial spastic paraplegia.*—Familial spastic paraplegia (FSP) is not a uniform entity either. It frequently begins in the first or second decade of life but may appear at any time. The duration of illness is long, usually more than ten years. Hereditary patterns may be either dominant or recessive. Certain cases show distal amyotrophy, especially in the upper extremities, and are therefore thought to be related to ALS, although the group is more often considered closer to the spinocerebellar degenerations. Clinical studies of FSP with amyotrophy, often associated with other severe neurologic abnormalities, were reported by Seeligmuller (1876), Gee

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(1889), Hoffmann (1894), Higier (1896), Maas (1904), Ormerod (1904), Holmes (1905), Pellizzi (1906), Jones (1907), Bruns (1912), Fearnsides (1912), Bremer (1922), Schaffer (1926), Gordon and Delicati (1928) Munch-Petersen (1931), Boeters (1939), Louis-Bar and Pirot (1945), Bickerstaff (1950), Garland and Astley (1950), Landau and Gitt (1951), van Bogaert (1952), and Refsum and Skillicorn (1954). Schwarz and Liu (1952, 1956) selected from the literature a few "acceptable" cases of FSP documented by pathological studies. They all showed involvement of the lateral corticospinal tracts, chiefly at thoracic levels, and demyelination of the fasciculi graciles. However, there was never clinical evidence of posterior column involvement. The lateral and anterior columns were diffusely demyelinated, frequently with greater involvement of the dorsal spinocerebellar tracts. In some, degeneration of neurones in the anterior horns and Clarke's columns occurred but was not clinically evident.

Our cases resembled FSP in respect to the hereditary pattern and the demyelination of the lateral and anterior columns of the spinal cord. The definite demyelination of the posterior columns in FSP was not in the same pattern as the posterior column demyelination in our cases but did resemble that seen in other hereditary and non-hereditary cases of ALS (*vide supra*). The short duration of illness and severe clinical and pathological involvement of the lower motor neurones which occurred in our cases are rarely if ever seen in FSP.

(3) *Neurogenic muscular atrophies beginning at an early age.*—Infantile spinal muscular atrophy usually has a subacute course with severe involvement of the lower motor neurones and occasional involvement of the lateral and posterior columns. The early age of onset, most often within the first year of life, and the lack of a dominant pattern of inheritance distinguishes it from the cases presented in this report.

Cases in the literature considered as "juvenile amyotrophic lateral sclerosis" do not comprise a uniform group. Some are types of spinocerebellar degeneration. Others are examples of familial spastic paraplegia with amyotrophy. A few are like those cases which were described by Wohlfart, Fex, and Eliasson (1955) and Kugelberg and Welander (1956) in which a very slowly progressive neurogenic muscular atrophy at spinal levels began at age 2–20 years and showed a recessive pattern of inheritance (autopsy data were not available). The remaining cases are similar to ALS clinically and pathologically, but differ from the cases presented herein in their earlier age of onset and their prolonged course of illness.

Also similar to juvenile ALS are cases of progressive external ophthalmoplegia due to lower motor neurone involvement. In these cases there may be concomitant neurogenic atrophy of other brain-stem and spinal musculature. The early age of onset and prolonged course distinguish these cases from the ones presented in this report.

(4) *Subacute combined degeneration.*—The disease (in contrast to the

pathological syndrome) of subacute combined degeneration (SACD) of the spinal cord is generally considered one of vitamin B_{12} deficiency and therefore should be arrested by adequate parenteral B_{12} therapy. With proper laboratory studies of gastric acidity, blood, bone-marrow, and metabolism of vitamin B_{12} tagged with Cobalt 60 (Schilling test), and with a therapeutic trial of parenteral vitamin B_{12}, the diagnosis can be established. The disease usually begins in later adulthood, is subacute in duration, and manifests megaloblastic anæmia, spasticity, and peripheral nerve and posterior column sensory loss. Pathologically, there is demyelination of the lateral columns and of the posterior columns, sometimes most severe in the middle root zones. The association of slight to moderate amyotrophy with SACD has been reported by Holmes (1913), Stone (1931), and Wilson (1955). Matarazzo and D'Orio (1954) reported amyotrophy, fasciculations, and spasticity with a macrocytic anæmia, all of which improved with parenteral B_{12} therapy. None of these authors noted hereditary factors in their cases, although Mosbech (1953) stated that SACD can show a pattern of recessive inheritance. Our cases were similar to SACD in regard to the age of onset, duration of illness, and pattern of demyelination in the cord. Unlike SACD, our cases showed severe lower motor neurone involvement, no sensory loss, and in at least one family, a dominant pattern of inheritance. Blood examinations, gastric analyses, and therapeutic trials with large parenteral doses of vitamin B_{12} disclosed no evidence of B_{12} deficiency. Schilling tests were not done.

Conclusions

Members of two families described in this report manifested a disease that bore clinical and pathological resemblance to amyotrophic lateral sclerosis. The two features unlike those of the usual cases of ALS were the pattern of dominant inheritance and the involvement of the posterior columns. It was emphasized that, although uncommon, a dominant hereditary pattern has been demonstrated in ALS. Demyelination of the posterior columns in both sporadic and hereditary cases of ALS has also been reported. This demyelination is more frequently confined to the fasciculi gracili, but in some instances (sporadic and hereditary) is located in the middle root zones. Although several hereditary neurological disorders with certain features similar to the cases described herein were considered, ALS is the one to which our cases seem most comparable.

The posterior column demyelination in the cases presented was most severe in the middle root zones. These zones are also selectively involved in other conditions. The only definite individual characteristic of these zones is that they are the earliest myelinated part of the posterior columns. It is tempting to suppose that diseases showing selective involvement of the middle root zones might have, at the biochemical level, a similar pathogenesis. One immediate objection is that these diseases, on other occa-

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sions, involve the posterior columns in a pattern which is not that of the middle root zones.

In regard to the cases presented, it is presumed that there was a dominantly inherited (genetically determined) metabolic failure, primary or secondary, to maintain the normal function and structure of the neurone cell body and processes—an abnormality so severe that after first manifestation in adulthood it caused death of the patient in six months to two and a half years.

Available evidence suggests that the cases in the two families described in this report manifested a hereditary disease not unlike amyotrophic lateral sclerosis. In order to definitely classify these cases and others like them as ALS, it must be determined that they represent a clinical variation of ALS caused by the action of modifying factors, largely genetic, upon the same basic abnormality as that in the more usual cases of ALS.

The presence in our cases of certain features infrequently noted in ALS but occurring more commonly in other inherited neurologic conditions suggests that these cases may represent an intermediate form of disease and thereby demonstrate a close relationship of the other conditions to ALS. This possibility can be neither confirmed nor denied on the basis of evidence presently available. Further elucidation of possible relationships of the underlying abnormality in the cases presented to the abnormalities in other inherited neurologic disorders with similar clinical and pathological features is required. Only with additional information can it be determined whether these cases are examples of an intermediate form of disease constituting a link in a continuum between ALS and certain other inherited neurologic disorders.

Summary

(1) An inherited neurologic disorder clinically indistinguishable from amyotrophic lateral sclerosis (ALS) occurring in two families is reported. In the first family there were at least 11 affected persons representing four generations; in the second family there were 3 affected persons representing two generations.

(2) The genetic pattern in the first family was that of an autosomal dominant trait having complete penetrance and in the second family was compatible with either a dominant trait having incomplete penetrance or a recessive trait.

(3) Pathological examination of 1 case in the first family and 2 cases in the second family revealed severe degeneration of lower and upper motor neurones. In addition, all 3 cases showed similar patterns of demyelination of the middle root zones of the posterior columns in the spinal cord. It appeared that the fibres myelinated earliest in the posterior columns were the ones most severely demyelinated.

(4) The cases presented were compared to ALS and to other inherited

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neurologic disorders. On the basis of available evidence, it was concluded that our cases probably represent a variant of ALS. However, there is no information on the basic abnormality in these cases and its possible relationship to the underlying abnormality in ALS and to the abnormalities in other inherited neurologic disorders. Therefore, it is impossible to determine whether the cases reported represent an intermediate form of disease which links ALS to certain other inherited neurological conditions as closely related members of a continuum.

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FIG. 3.—Sections of the spinal cord at A cervical, B thoracic, and C lumbar levels from patient V-56 in Family A. Smith-Quigley stain for myelin.

To illustrate article by W. King Engel, Leonard T. Kurland and Igor Klatzo.

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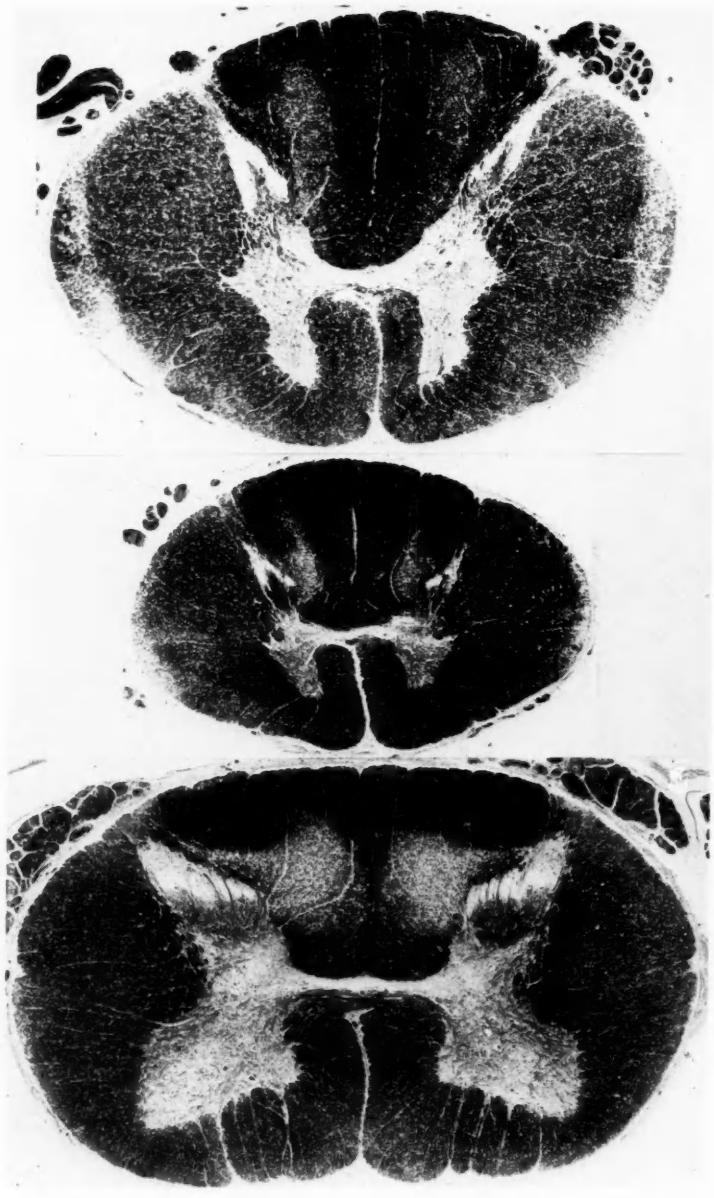

FIG. 4.—Sections of the spinal cord at A cervical, B thoracic, and C lumbar levels from patient IV-4 in Family B. Smith-Quigley stain for myelin.

To illustrate article by W. King Engel, Leonard T. Kurland and Igor Klatzo.

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OBSERVATIONS ON ENDOCRINE FUNCTION IN DYSTROPHIA MYOTONICA

BY

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THE frequent occurrence of cataract, frontal baldness, impotence, loss of sexual desire, testicular atrophy or amenorrhœa in patients suffering from dystrophia myotonica has always suggested that the muscular disorder may be related to endocrine dysfunction. The results of the endocrine studies which have been reported in the past, though not entirely negative, have been disappointing, in that they failed to establish any ætiological relationship between the muscular disorder and such endocrine abnormalities as were present. A constant finding has been a low basal metabolic rate, but the uptake of radioactive iodine by the thyroid gland and measurement of the serum protein-bound iodine have been normal (Jacobson, Schultz and Anderson, 1955; Holland and Hill, 1956), suggesting an extra-thyroid cause for the low metabolic rate. Decreased urinary excretion of 17-oxosteroids has likewise been consistently reported (Caughey and Brown, 1950; Nadler, Steiger, Troncelleti and Durant, 1950; Jacobsen *et al.*, 1955; Holland and Hill, 1956; Clarke, Shapiro and Monroe, 1956). Urinary gonadotrophin excretion, on the other hand, has varied from study to study; Jacobsen *et al.* (1955) and Holland and Hill (1956) found it to be normal, whereas Caughey and Brown (1950) and Nadler *et al.* (1950) reported it to be increased in some of their cases. Clarke *et al.* (1956) found the excretion of "follicle stimulating hormone" (FSH) to be normal but that of the "luteinizing" or "interstitial cell stimulating hormones" (ICSH) to be raised in 2 male patients. Most authors have found that testicular biopsy showed atrophy of the seminiferous tubules and cells of Sertoli, with normal interstitial cells (Leydig cells) and sometimes an apparent increase in the latter. Studies of parathyroid and adrenal gland function in the main have been negative.

Despite the negative correlation between the endocrine and muscular aspects of the disease in previous studies, there appeared to be several

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reasons for re-examining these relationships at the present time. The first was the development of new and more reliable methods of estimating œstrogens (œstrone, œstradiol-17β and œstriol) and pregnanediol in the urine, methods which have not been applied previously to the study of this disease. Since these substances are, at any rate in part, of gonadal origin, it seemed justifiable to attempt to relate disturbance in their production to the muscular wasting and other features of the disease. The second reason was to apply more reliable methods of estimating pituitary gonadotrophins to the problem, and to attempt to explain the very variable and conflicting results reported in previous studies. The third was to examine patients at a less advanced stage of the disease in order to establish the order of events, muscular and endocrine, in the development of the disease. It seemed possible that the endocrine failure commonly observed in the late stage of the disease is but a sequel to a degenerative disorder involving many tissues, rather than a causative factor in the disease. Moreover, the discrepancy in the previous findings, with regard to the gonadotrophins, might also be due to the stage of the disease at which the estimations were made.

Case Reports

Case 1 (*M.N.* 522)

The patient was a single man, aged 34 years. For fifteen years he had noticed that his leg muscles tightened on sudden movement and caused him to fall. More recently he had noticed weakness of the lower limbs. He was reticent about his sexual functions. His father had died of injuries, his mother had a cataract and his sister was alive and well. On examination there was extensive baldness, but the body hair was normal. He had bilateral facial weakness and ptosis and severe wasting and weakness of the sternomastoids. There was distal wasting and weakness of both upper and lower limbs. Tendon reflexes were difficult to obtain, the plantar responses were flexor and there was no sensory abnormality. Myotonia was demonstrable in the muscles of the hands. His testes were abnormally small.

Case 2 (*M.N.* 563)

The patient was a single man, aged 41 years. At the age of 26 years he had noticed weakness of grip when playing tennis and by the time he was 31 years could no longer play because of this. He next noticed that he was catching his toes when he walked, this symptom developing when he was 38 years old. He had had no nocturnal emissions for sixteen years. On examination there was marked frontal baldness but the body hair was normal. There was bilateral weakness of facial muscles, with ptosis and slight slurring of speech. The sternomastoids were wasted and weak. There was wasting and weakness of the forearm muscles with severe myotonia. In the lower limbs there was general wasting, with weakness of the dorsiflexors of both feet. All tendon reflexes were difficult to obtain, the plantar responses were flexor and there was no sensory abnormality. His testes appeared normal to palpation. His father had died of tuberculosis when young; his mother and two siblings were alive and well.

Case 3 (*M.N.* 889)

The patient was a married man, aged 45 years. For many years he had noticed progressive weakness of arms and legs. He had previously been a butcher, but had

not worked for nine years because of his weakness. He apparently had lost his sexual power many years previously. His father and mother died in old age without cataract or muscular disorder, his brother was well but his sister was known to have dystrophia myotonica. He had a son aged 14 years who was well. On examination he had frontal baldness, bilateral ptosis and wasted sternomastoids. There was no wasting of muscles elsewhere but his limbs were weak. The tendon reflexes were sluggish, plantar responses flexor and there was no sensory abnormality. His testes were abnormally small to palpation. There was no demonstrable myotonia.

Case 4 (*M.N.* 1181)

The patient was a single man, aged 50 years. He had complained that for ten years he had noticed progressive weakness of upper and lower limbs and had difficulty in raising his head from the pillow. On examination he had extensive baldness, but normal body hair. There was marked weakness of facial muscles with bilateral ptosis and slurred speech. His general musculature was very poorly developed and there was severe weakness of all muscle groups in both upper and lower limbs, with myotonia. Tendon reflexes were unobtainable, the plantar responses were flexor and there was no sensory abnormality. His testes were abnormally small to palpation. His father and mother died at 77 years without cataract or muscular disease; three siblings had died young from unrelated causes, two others were alive and well, but one sister, though not weak, "could not let go of things."

Case 5 (*M.N.* 348)

The patient was a single woman, aged 38 years. At the age of 15 years she had noticed slurring of speech, but beyond this was well until the age of 35 years when she gradually developed weakness of both legs. Her menses were still regular, lasting five days every twenty-eight days. On examination she had bilateral weakness

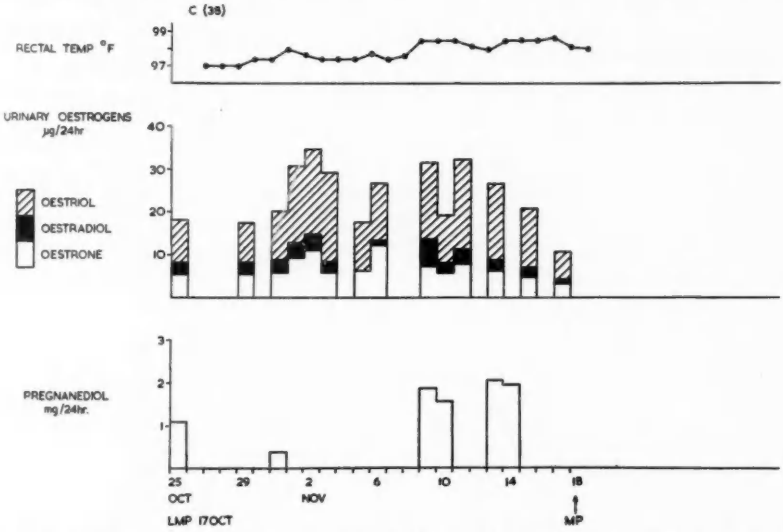

FIG. 1.—Excretion of œstrone, œstradiol-17β, œstriol and pregnanediol by Case 5 throughout three weeks of a menstrual cycle. M.P.=first day of menstrual period. L.M.P.=first day of last menstrual period.

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of facial muscles and weakness of her palate. The sternomastoids were wasted and weak. There was slight weakness of grip in both hands, with marked myotonia. In the lower limbs there was weakness of the dorsiflexors of both feet. The tendon reflexes were all present, the plantar responses flexor and there was no sensory abnormality. The distribution of body hair was normal. Her father and sister, who were not examined, were reported to have "muscular trouble of the same kind."

Case 6 (*M.N.* 148)

The patient was a married woman aged 50 years. Ten years previously she had noticed a change in the tone of her voice and difficulty in clearing her throat. Five years later, she had developed heaviness and later, progressive weakness of her legs. Three years before the study, her arms gradually became weak and she noticed she could not raise her head from the pillow. Two years later, she began to have difficulty in swallowing. Eight years before observation she had a hysterectomy for fibroids, up to which time her menses had been regular. Her father and mother died at 80 years and 64 years respectively without cataract or muscular disorder; two siblings had died of unrelated causes and two were alive and well. She had two children, aged 31 and 21 who were well, and one had died in infancy of tuberculous meningitis. On examination her body hair was normal. The palate appeared to move well but her cough was weak and she had obvious dysphagia. The sternomastoids showed gross atrophy. The muscles of both upper and lower limbs were wasted and weak, especially distally, and there was marked myotonia. Tendon reflexes were present, plantar responses flexor and there was no sensory abnormality.

Case 7 (*N.H.* 74993)

The patient was a single man, aged 41 years. Thirteen years previously he had noticed weakness of the arms, and three years later, weakness of the legs. These symptoms progressed until he could walk only with assistance. As long as he could remember, he had difficulty relaxing his grip, and for many years had lost all sexual power. His father died in his sixties, and had had weak muscles and could not relax his grip. His mother and three siblings were alive and well. On examination there was frontal baldness and sparse pubic and axillary hair. There was bilateral facial weakness and ptosis, and gross wasting and weakness of the sternomastoids. All limb muscle groups were wasted and weak, the reflexes were sluggish or absent, the plantar responses unobtainable and there was no sensory loss. Severe myotonia was present. The left testicle was normal to palpation, the right testicle was only half the size of the left.

Case 8 (*N.H.* 74911)

The patient was a married man of 54 years. His history was obscure as he insisted on dating his symptoms to the time of an explosion three years previously. His complaints were of weakness of the arms and legs, drooping of the eyelids and difficulty with his speech. His father was alive and well, his mother had died at 73 years without muscular disorder or cataract, one sibling had died in adolescence of meningitis and one was alive and well. He had 3 children, all well. On examination he was bald, had sparse axillary but normal pubic hair. There was bilateral ptosis and facial weakness with wasting and weakness of the sternomastoids. The upper limbs were wasted and weak, the tendon reflexes were sluggish, the plantar responses were flexor and there was no sensory abnormality. The testes were normal to palpation, and the thyroid was diffusely enlarged. The posterior tibial and dorsalis pedis pulses were absent and there were ischaemic changes in the skin of the feet.

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Case 9 (*N.H.* 73531)

The patient was a single man, aged 26 years. For ten years he had noticed difficulty in relaxing his grip after strenuous contraction, and for eight years difficulty in articulation. He was reticent about his sexual functions. He came from an extensive family, several of whom were known to have dystrophia myotonica. On examination there was slight recession of the hair-line from the forehead but normal body hair. There was minimal ptosis and facial weakness and slight atrophy of the sternomastoids. There was no wasting or weakness of the limb musculature but obvious myotonia. The tendon reflexes were absent, the plantar responses flexor, and there was no sensory abnormality. His testes were normal to palpation.

Case 10 (*N.H.* 74714)

This patient was a single woman, aged 28 years. Three years previously she noticed weakness of the lower limbs and two years later, weakness of the upper limbs, together with difficulty in relaxing her grip. Her menses were of four or five days' duration every twenty-eight days. Her father died at 44 years of pneumonia and had been bald for as long as she could remember; he was always falling for no

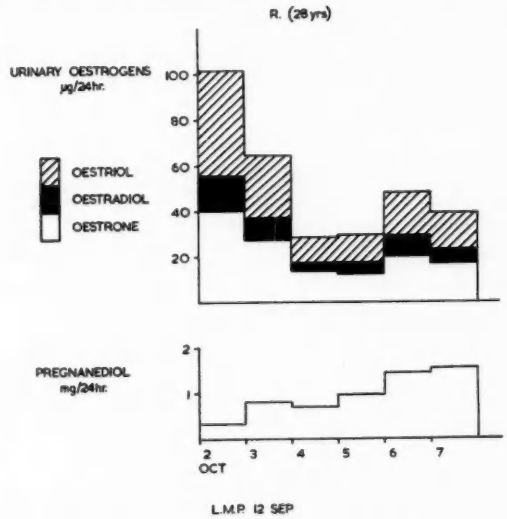

FIG. 2.—Excretion of œstrone, œstradiol-17β, œstriol and pregnanediol by Case 10 during the fourth week of a menstrual cycle. L.M.P.=first day of last menstrual period.

apparent reason. Her mother died at 54 years of "a heart attack" and had no muscular disorder or cataract. She had 3 siblings alive and well. On examination she had slight bilateral ptosis and facial weakness, with a slurring dysarthria. Both sternomastoids were grossly wasted and weak. There was peripheral wasting and weakness of muscles in both upper and lower limbs, with myotonia in the hand muscles. The tendon reflexes were sluggish, the plantar responses flexor and there was no sensory abnormality.

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Case 11 (*M.N.* 1258)

The patient was a 67-year-old married man who for twelve years had noticed progressive weakness of muscles with difficulty in relaxing his grip. His maternal grandmother, his mother, his sister and one of his sons were all known to suffer from dystrophia myotonica. Examination revealed frontal baldness with normal body hair. He had a myopathic facies. There was gross wasting and weakness of sternomastoids and peripheral muscles of upper and lower limbs, with loss of tendon reflexes. The plantar responses were flexor and there was no sensory loss. Severe myotonia was present in the small muscles of the hand. The testes were normal to palpation.

Methods

The following methods were used in making the estimations described.

(1) Radio-iodine test of thyroid function
  Patients marked (*a*) in table: Mason and Oliver (1949).
  „ „ (*b*) in table: neck uptake of ^{131}I.
(2) Pituitary gonadotrophins: Loraine and Brown (1959).
(3) Œstrogens: Brown (1955*a*).
(4) Pregnanediol: Klopper, Michie and Brown (1955).
(5) 17-oxosteroids: King and Wootton (1956).
(6) 17-hydroxycorticosteroids: Appleby, Gibson, Norymberski and Stubbs (1955).
(7) Basal metabolic rate: Benedict Roth spirometer, using the standards of Aub and Du Bois (1917).

Results

The findings in this investigation are recorded in Table I. The concentrations of sodium, potassium, chloride and alkaline phosphatase in serum and of the plasma proteins were within the normal range. In 2 patients single estimations of the serum calcium concentration slightly exceeded 11 mg. per 100 ml. and in a third patient the serum inorganic phosphorus concentration was abnormally low. The blood cholesterol estimations were within the normal range, with the exception of Case 3, in whom it was found to be raised, but this was associated with a normal radio-iodine test. In 4 of the 6 patients in whom the estimation was made the basal metabolic rate was low; in 3 of these remarkably so.

Radio-iodine tests were normal in 9 and low in 2 patients. The test was repeated in 2 patients (Cases 3 and 4) after the administration of thyrotrophic hormone (Thytropar, Armour and Company). In Case 3 the result remained normal but in Case 4, who had a nodular goitre, the whole thyroid became swollen, painful and tender. During the eight hours after the administration of radio-iodine, only 0·2 per cent of the test dose was excreted in the urine, but thereafter the amount was large compared with the usual findings following the injection of thyrotrophin. The pain, tenderness and swelling of the gland had virtually subsided within twenty-four hours. The patient's response to thyrotrophin was therefore abnormally vigorous and unusually short-lived.

The glucose tolerance test was normal except in Cases 2 and 5, where

a flattened curve was observed and the insulin tolerance tests were likewise normal except in Case 8, who appeared to be somewhat resistant to insulin.

17-oxosteroid (ketosteroid) excretion was low in each patient in whom estimations were made, with the single exception of Case 11. Œstrogen excretion by two female patients (Cases 5 and 10) was within the normal range (Brown, Klopper and Loraine, 1958) and the amount excreted by the male patients, both in total quantity and in the relative proportions of œstrone, œstradiol-17β and œstriol was also normal (Brown, 1955*b*). Pregnanediol excretion in the cases examined was normal, both in the 2 female patients whose menses were normal (Klopper, 1957) and in the males (Klopper, Strong and Cook, 1957). Gonadotrophin excretion was within the normal range in all patients studied (Loraine, 1957).

Testicular biopsies were performed in 6 patients. The histological findings were abnormal in each, with the exception of Case 11, hyaline degeneration of seminiferous tubules occurring along with normal interstitial cells. In 3 instances, histologically normal tubules adjoined others which were grossly diseased, and in Case 3 there was uniform tubular degeneration in the biopsy specimen. Nuclear chromatin material of the type described by Barr and Bertram (1949) was not observed in any of the biopsies available for examination.

Discussion

This investigation was designed to study some of the endocrine disturbances known to occur in patients with dystrophia myotonica. These disorders are inconsistent in severity and occurrence, and an attempt was made therefore to seek correlations which might exist between different forms of abnormal endocrine function and to relate these to the clinical findings.

The basal metabolic rate was unusually low in 3 of the 6 patients, a finding which has been reported frequently in other studies. An unusual feature, however, was the association of a low radio-active iodine test in 2 of the patients, suggesting depression of thyroid function. It has been suggested that the low basal metabolic rate is due to extra-thyroid causes, the degree of muscle wasting in relation to the extent of the body surface influencing the estimation of the BMR. The findings in these 2 cases make this interpretation doubtful, though it must be pointed out that none of the patients showed any clinical evidence of depressed thyroid function. Estimation of the serum concentration of protein-bound iodine would have been of considerable value but was not available.

The remarkable response to the administration of thyrotrophic hormone in Case 4 cannot be explained at the present time. The clinical findings suggested a form of thyroiditis which subsided rapidly when the thyrotrophin was withdrawn. The radio-iodine test indicated an

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abnormally brisk but ill-sustained response by the gland, which would be surprising if the swelling were inflammatory, as acute or subacute thyroiditis is usually associated with reduced uptake of radio-iodine by the inflamed gland.

A number of tests, both direct and indirect, were employed to assess the secretory activity of the adrenal cortex. Apart from the absence of symptoms and physical signs of adrenocortical insufficiency, there was much indirect evidence of normal adrenocortical function. This included the electrolyte findings, the tests of carbohydrate metabolism, namely the glucose tolerance test and the insulin sensitivity test, and the Kepler test (Robinson, Power and Kepler, 1941). Moreover, the total 17-hydroxycorticosteroid excretion which was measured in 2 patients was normal or, in Case 9, somewhat high, suggesting if anything some increase in adrenocortical activity. Certainly there was no indication of any degree of adrenal insufficiency.

The secretion of œstrogens in the patients of this series was within the normal range. Œstrogens are secreted by the functioning ovary, by the adrenal cortex (Brown and Strong, 1958) and probably by the testes. The assay method employed in this study (Brown, 1955*a*) determines the amount of œstrone, œstradiol-17β and œstriol in the urine but does not estimate 6 other more recently discovered urinary œstrogen metabolites (Marrian, 1958). The assays show no sign of abnormal œstrogen excretion in the patients of either sex, and the fluctuations of œstrogen excretion during the menstrual cycles of Cases 5 and 10 are similar to those reported during the normal cycle (Brown, 1955*b*; Brown, Klopper and Loraine, 1958). Pregnanediol, a metabolite of progesterone, is excreted as a result of both ovarian and adrenocortical activity (Klopper, Strong and Cook, 1957). In the patients in whom the estimation was made, pregnanediol excretion was normal. Hence, as has previously been shown with other hormone products, abnormalities of œstrogen and pregnanediol secretion do not appear to be the cause of the muscular disorder.

Estimations of pituitary gonadotrophins in urine in 5 of the 6 male patients showed that excretion was normal or low. This important difference in gonadotrophin excretion between these patients and some of those reported in other studies can be explained in at least two ways. In the first place, results reported in the past have usually been obtained by methods which can only be regarded as semi-quantitative. Secondly, it is possible that the gonadotrophin excretion reported in male patients may be related to the condition of the testes. For example, in 2 of Caughey and Brown's (1950) patients in whom satisfactory testicular biopsies were obtained there was extensive tubular degeneration as well as virtual disappearance of interstitial cells. In both of these patients (Case 1, F. A. M., and Case 8, J. B.) gonadotrophin excretion was found

to be abnormally high. In a third patient with a high gonadotrophin excretion, testicular biopsy was unsatisfactory. In the fourth male patient examined gonadotrophin excretion was considered to be normal, but testicular biopsy was not performed; the testes were, however, noted to be apparently normal. Although there was evidence of tubular degeneration in each of the testicular biopsies from our patients in whom gonadotrophin assays were performed, this was usually seen in irregular patches between areas showing normal tubules. There was no histological evidence of damage to the interstitial (Leydig) cells and in no patient was the excretion of gonadotrophins abnormally high. Increased gonadotrophin excretion by male patients with this disease is associated, therefore, with extensive testicular degenerative changes, and although the abnormal excretion of gonadotrophin reported by others may have been due to the limitations of the assay method used, it is more probable that the severity of the changes in the testes was the determining factor.

Evidence of gonadal failure is provided in the present series by the low excretion of 17-oxosteroids in male patients. These steroids are of adrenocortical as well as testicular origin, but in view of the absence of any clinical or biochemical evidence of adrenocortical insufficiency, their low output may be accepted as further evidence of testicular failure. On the other hand, histological examination showed that the gonadal atrophy mainly affected the seminiferous tubules; the appearance of the interstitial cells, which are believed to produce the steroid precursors, was normal.

Thus the high gonadotrophin excretion previously reported was probably a consequence of testicular atrophy, since when this is not advanced the gonadotrophin excretion appears to be normal. It seems unlikely, therefore, that a disturbance of production of pituitary gonadotrophin is in any sense a cause of the disease.

It is difficult to formulate an adequate hypothesis to explain these data. Primary general pituitary failure cannot be responsible in view of the normally functioning endocrine glands, and the normal excretion of pituitary gonadotrophins. The raised excretion of pituitary gonadotrophins in previous studies appears to be secondary to gonadal failure. The possibility of primary gonadal failure is raised by the low output of 17-oxosteroids. The degree of failure at any particular stage of the disease as measured by the 17-oxosteroid excretion, the secondary rise in pituitary gonadotrophin excretion and the histological appearances seen in testicular biopsies is clearly highly variable. Moreover, in the female patients the excretion of œstrogens may be quite normal at a stage when the muscular disease is advanced. A primary gonadal atrophy as the cause of the disease seems, therefore, most unlikely.

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Rather both the muscular and endocrine aspects of the disease appear to result from a cause or causes still unknown.

Summary and Conclusions

(1) 11 patients (8 male, 3 female) suffering from dystrophia myotonica have been studied from the point of view of endocrine function.

(2) In 2 patients (1 male, 1 female) there was evidence of reduced thyroid function, and in both of these, the glucose tolerance test was unusually flat.

(3) Testicular biopsy was performed in 5 patients and in 4 of these there was evidence of tubular degeneration.

(4) Hormone assays performed on urine samples included pituitary gonadotrophins, 17-oxosteroids, total 17-hydroxycorticosteroids, œstrone, œstradiol-17β, and œstriol, as well as pregnanediol. The excretion of 17-oxosteroids was low; the excretion of pituitary gonadotrophins was normal or low in contrast to previous reports of increased excretion.

(5) The findings fail to indicate any correlation between the disease and the excretion of the hormones named.

Acknowledgments

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VISUAL DISCRIMINATION FOLLOWING SUCCESSIVE TEMPORAL ABLATIONS IN MONKEYS

BY

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INTRODUCTION

PERFORMANCE on a variety of visual perceptual tasks may be disturbed following injury or disease of the so-called "association areas" of the cortex in man. Thus impairment may commonly be elicited by tests of sorting and classification (Teuber, Battersby and Bender, 1951; McFie and Piercy, 1952); or when the patient is required to distinguish between "figure" and "ground" (Teuber and Weinstein, 1956); or even on the less complex tests of discrimination between dissimilar stimulus figures (Battersby, Krieger and Bender, 1955). However, location of the cortical lesion would not seem to be an important determinant of the deficit on any of these tests in man. Nor yet are such disorders of perception a regular consequence of a lesion in the association cortex.

A different conclusion concerning the necessary site of the lesion may be drawn when clinical impairment on tests of "spatial perception" is considered. Thus the disorders termed "apractognosia" (Hécaen, Penfield, Bertrand and Malmo, 1956), "amorphosynthesis" (Denny-Brown and Banker, 1954) and "visual-spatial agnosia" (Ettlinger, Warrington and Zangwill, 1957) have been generally reported to follow lesions situated in the posterior parietal areas. This same site of injury has been implicated for impairment on a quantitative test of spatial orientation in an unselected series of cases (Semmes, Weinstein, Ghent and Teuber, 1955). However, the earlier view that such disorders of spatial perception were specific to the visual modality can no longer be sustained (Ettlinger *et al.*). In fact "the parietal group showed a slightly greater percentage decrement on the tactual maps than on the visual series" (Semmes *et al.*). It would therefore appear that no consistent relationship has as yet been established in an unselected series of clinical cases

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between a disorder of perception[1] confined to the visual sensory modality and any one site of lesion within the association cortex.

It is in part by contrast to these current clinical findings that the visual deficit occurring in monkeys as a consequence of bilateral temporal lesions merits further consideration. For this impairment can be expected to follow the appropriate specifiable lesion virtually without exception. Moreover animals giving evidence of this visual deficit are unimpaired under comparable conditions of somato-sensory and auditory testing (Pribram and Barry, 1955; Wilson, 1957; Weiskrantz and Mishkin, 1958; Wegener, 1959). It might also appear unexpected, if not paradoxical, on general principles of progressive encephalization of function that a behavioural deficit should be linked with a lesion to a small part of the cortex more reliably in the monkey than in man. Therefore the disorder of visual perception in monkeys with temporal ablations may still perhaps at some future time be called upon to serve rather as a paradigm for, than contrast to, the clinical observations of perceptual disruption in man.

A comparison between this "psychic blindness" in monkeys and an extraordinarily rare clinical condition, the associative mind-blindness of Lissauer, was already drawn by Klüver and Bucy in 1938 (just as Lissauer had traced similarities between his clinical instances and the animal preparations of Munk.) A more detailed quantitative analysis of the behavioural changes in monkeys was presented by Blum, Chow and Pribram in 1950. Thereafter the more precise delineation both of the smallest effective lesion and also of the behavioural consequences followed rapidly. For example the studies of Chow (1952) and Mishkin (1954) indicated that bilateral removal of the inferior temporal surface is sufficient to reproduce the visual disorder. Moreover the emotional, dietary and sexual changes associated with the more radical lobectomy procedure of Klüver do not occur following this limited infero-temporal cortical ablation. Instead they can be correlated with damage to other sectors of the temporal lobe. On the other hand a *unilateral* temporal lobectomy or cortical ablation was found to be not sufficient to give rise to any appreciable visual deficit (Mishkin and Pribram, 1954).

As a rule the animals' visual perception has been assessed by means of the two-choice discrimination procedure in which one of two dissimilar cues is consistently rewarded irrespective of its position. Animals with bilateral temporal excisions were then impaired whether the cues differed in hue, brightness, size or form (Mishkin and Hall, 1955), provided only that the test exceeded an intermediate level of difficulty (as determined by reference to the performance of unoperated animals on a series of

[1]In the present context the term "perception" is held to apply neither to the unlearnt optokinetic response (Carmichael, Dix and Hallpike, 1954) nor to tests of "visual intelligence" (Milner, 1954).

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tasks). This post-operative impairment became evident both during re-learning of a discrimination originally acquired before surgery and during initial post-operative acquisition of a discrimination. However, the incidental field defects, following some but not all of the temporal lesions, or possible areas of amblyopia could not, it was claimed, be held responsible for this comprehensive visual perceptual disorder. For dissimilar patterns of breakdown on a variety of visual tasks resulted from a comparison between the effects of infero-temporal excisions and of striate lesions involving the cortical macula. For example the striate animals were inferior to temporal animals on a test of the difference threshold for visual size, whereas the temporal animals were inferior to the striate animals on a standard test of visual discrimination learning (Wilson and Mishkin, 1959). Nor yet can this visual disorder be attributed to any simple impairment of learning or of "immediate memory" confined to the visual modality. For temporal animals may achieve a higher standard of performance than do control animals on tests of delayed reaction in which correct choice of response depends upon learning to remember the nature of an immediately preceding cue (Pribram and Mishkin, 1956).

Bilateral infero-temporal ablations in monkeys would then seem to have as their consequence a widespread disorder of perception that is specific to the visual modality (since somato-sensory and auditory discrimination remain unimpaired). Loss of sensory capacity as a result of field defects appears neither sufficient nor necessary to give rise to the deficit. Nor yet has general learning ability or immediate memory become defective in these animals. The disturbance following temporal lesions is not therefore obviously dependent upon disruption of any one or more of the functions that would appear *a priori* to be concerned in visual discrimination by the intact animal.

Before resorting to more complex interpretations it was nevertheless thought advisable to examine what contribution *qualitative* or *relative* changes in elementary visual sensory efficiency might make to the genesis of this perceptual disorder. For it could be argued that previous studies had succeeded in excluding the ætiological significance only of relatively dense or absolute field defects. Moreover even areas of absolute blindness cannot be easily charted in the monkey, so that qualitative or relative sensory changes might readily escape detection. Also some indirect support for this point of view was thought to be forthcoming from studies of somato-sensory discrimination. Thus a disturbance in this modality has been reported to occur as a result of bilateral parietal lesions in monkeys, and has been regarded as analogous to the visual disorder following temporal excisions. When animals were tested on a variety of somato-sensory discriminations separately with each hand after *seriatim* removals of the temporo-parietal areas, the

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performance with the two hands was found to differ unexpectedly (Blum *et al.*). For performance with the first hand to be tested following surgery (that is, with the post-operatively preferred hand, being on the side opposite to the first lesion) was usually superior to that achieved with the second hand to be tested (that is, with the post-operatively non-preferred hand, being on the side opposite to the second lesion). These results were obtained although the discrimination had been acquired pre-operatively with the hand giving the inferior post-operative performance. They are contrary to the expectation of improvement in performance with the second hand following prior post-operative relearning with the other. It would, in fact, almost seem as if the two hands operate independently in relearning a somato-sensory discrimination following bilateral parietal lesions.

An investigation was therefore undertaken to determine whether qualitative or relative alterations in elementary visual sensory capacity might account for the defect of visual discrimination in temporal monkeys. The assumption was made that such (modality-specific) changes would take place only in the visual half-fields opposite to a unilateral lesion. Then the previously demonstrated absence of impairment consequent upon unilateral temporal ablations would be comparable to the absence of impairment expected as a consequence of a unilateral lesion giving rise to a complete homonymous hemianopia. On the other hand at least as severe a disturbance would be expected to follow a unilateral temporal removal made on the side of the brain opposite to a lesion causing a complete homonymous. hemianopia as would be expected to follow bilateral temporal removals. Again, the addition of a second temporal removal from the same side of the brain as the lesion causing the hemianopia would not be expected to give rise to further impairment. More specifically, it was predicted, firstly, that animals having a *left* unilateral temporal excision combined with a section of the *left* optic tract would remain unimpaired; secondly, that animals having a *right* unilateral temporal excision combined with a section of the *left* optic tract would be as severely impaired as animals having bilateral temporal excisions; and finally, that addition of a *left* temporal excision to pre-existing *left* tract and *right* temporal lesions would give rise to no further impairment. These predictions were put to experimental test.

METHOD

Subjects.—12 previously untrained rhesus monkeys served as subjects for this experiment. Their weights ranged from 5 to 6¾ lb. at the beginning of training, and from 6 to 7½ lb. at the time of the last surgical operation upon each animal.

Operations.—Surgical procedures were undertaken at 6 different sites of the brain. However, only one lesion was made at each operation (except in the case of the first operation upon animals 11 and 12). All animals received at least two lesions serially. The lesions comprised: total section of the left, or the right optic tract; aspiration of the

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left, or the right inferotemporal-preoccipital cortex; aspiration of the right antero-lateral frontal cortex; and total division of the corpus callosum.

All operations were performed aseptically under intraperitoneal nembutal anæsthesia. The optic tract was visualized from an anterior approach after removal of the zygoma and elevation of the temporal pole. It was then cut as far behind the chiasm as proved practicable. Silver clips were applied to the left tract behind the section in the case of animals 1 and 2. In animals 4 and 12 the right optic tract was cut three weeks and five months respectively after section of the left tract. This operation was considered essential in order to secure behavioural verification of the effectiveness of the left tract section in animals that had performed contrary to expectation on the pattern discrimination. Cortex was aspirated by means of a small-gauge sucker. The temporal removals were intended to reproduce the lesions made by Mishkin and Hall, that is, in brief, to extend ventrally and medially from the superior temporal sulcus, and reach backwards as far as the vein of Labbé and the inferior occipital sulcus. The frontal ablations were designed to extend forwards from the arcuate sulcus over the entire lateral surface. The frontal poles were amputated within an arc of about 2 cm. from their tips. Exposure of the corpus callosum required the coagulation of 3 large bridging veins to the longitudinal sinus on the left side. The callosum could then be divided along its entire length under full visual control by blunt dissection. This procedure was recognised to involve damage to the fornix and penetration into the third ventricle.

Histological procedures and findings.—Following completion of testing the animals were anæsthetized and their brains perfused with formalin, removed, examined macroscopically, and then prepared for histological study. Serial coronal sections of 50μ thickness were cut. Every tenth section was stained with thionin, and the remaining nine discarded except in the region of the optic tract transections, where selected sections were stained by the Loyez method.

The cortical removals were found to correspond in general to the surgical intentions, those in the left hemisphere being somewhat more extensive than those in the right. Macroscopically the optic tract sections were seen to be placed at between 2 mm. and 5 mm. behind the chiasm. It was found possible to verify by histological study that the left optic tract had been completely cut in all animals and that the corpus callosum was divided along its entire length in the 3 animals receiving this lesion.

Fig. 1 shows reconstructions of the cortical lesions and selected cross sections in representative cases (animals 2, 7 and 12). From the histological sections the extent of any incidental damage to structures in the neighbourhood of the transected tracts was determined.

In most of the animals the antero-inferior part of the left temporal lobe, including the amygdaloid nucleus, was involved as a consequence of displacing the temporal pole in dividing the optic tract. However, such damage extended on to the lateral surface only in the case of animals 3, 5, 6, 9 and 11, and in no instance sufficiently far backwards to encroach upon any cortex that would properly be included in an inferotemporal removal.

Section of the left optic tract also caused incidental damage in most animals to the globus pallidus, and to some fibres of the internal capsule. Other structures in the neighbourhood of the lesion showing occasional damage were as follows: the putamen; the habenula and hypothalamus; the ansa lenticularis; the anterior commissure; the caudate; the thalamus.

In 2 of the 3 animals in which the corpus callosum was cut, there was incidental damage to the cortex. In animal 3 a large area of degeneration was found in the left frontal lobe, extending from the central sulcus to within 1 cm. of the frontal pole, and from the superior arcuate sulcus over the medial surface of the lobe. A much smaller

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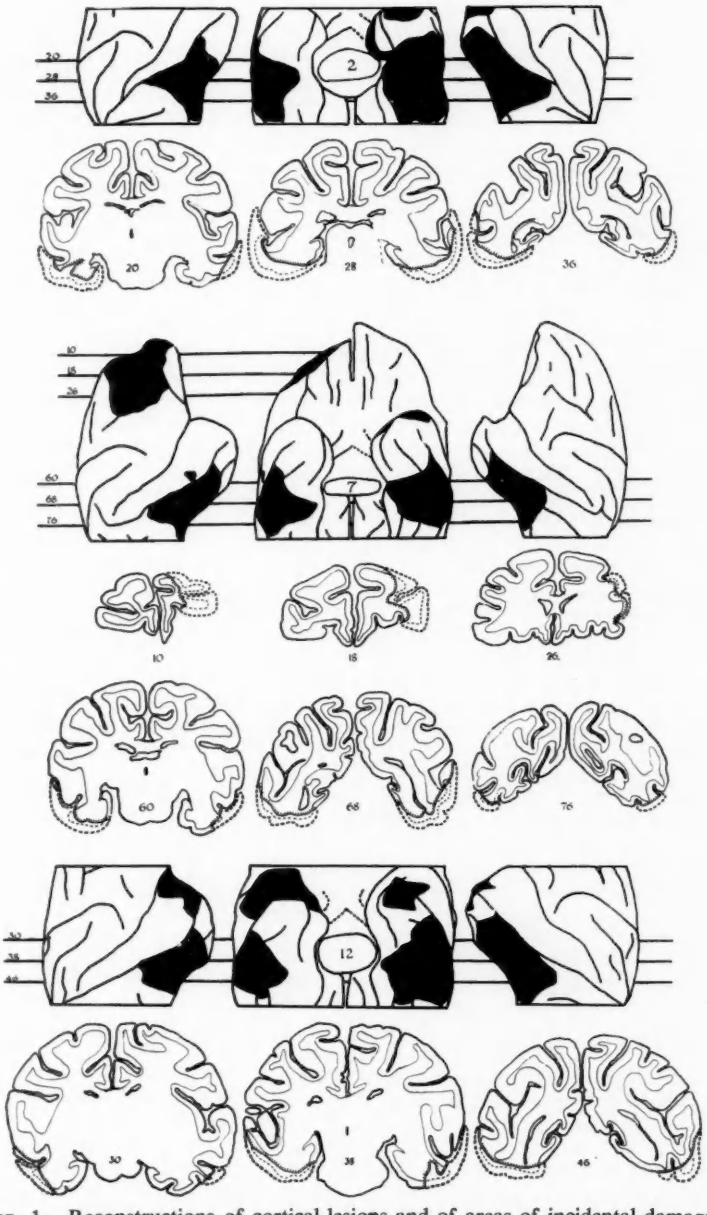

FIG. 1.—Reconstructions of cortical lesions and of areas of incidental damage in animals 2, 7 and 12, together with selected cross sections. Black indicates the extent of cortical damage in the surface views.

area of degeneration (about $\frac{3}{4}$ cm. in diameter) was seen in the left post-central parasagittal cortex of animal 6.

Apparatus.—The animals were wheeled to the testing room in a transport cage. They were able to grasp the cues from this cage by reaching through vertical bars spaced 2 in. apart. One of the 2 screens forming part of a large wooden enclosure surrounding the transport cage was always interposed between the animal and the experimenter. The forward one-way vision screen could be raised in between the transport cage and the cues to allow the experimenter to conceal the reward under either cue without the animals' knowledge. The rear one-way vision screen separated the experimenter from the cues when the forward screen was lowered. The animal could be observed at all times by means of this apparatus.

Tests.—All animals were taught to discriminate between an outline square and a cross. The outside edges of the square measured $1\frac{3}{4}$ in. and the inside edges were 1 in. long. The arms of the cross measured $1\frac{7}{8}$ in. tip to tip and were $\frac{1}{2}$ in. wide. These 2 patterns were painted in yellow on the grey lids ($2\frac{3}{4}$ in. $\times$ 4 in.) of food boxes set 12 in. apart on a horizontal shelf. Correct response consisted in pushing the lid with the square painted on it away from the cage to give access to the contents of the food box. A peanut could then be taken from the box and served as reward. Thirty trials were given each day and training was continued until the animal reached an arbitrary standard of performance. This standard consisted in making 10 or less errors in 100 consecutive trials. These last 100 trials are not included in the test scores, according to convention. The final score therefore represents the number of trials in excess of 100 required to achieve the standard level of performance (10 or less errors in 100 trials). The left/right positions of the positive cue (square) were randomized in accordance with a balanced schedule and non-correction procedure was used except in the rare event of a severe position habit (that is 10 consecutive responses to the same side). In that case the positive cue was maintained on the alternate side and the animal was allowed to correct 1 in 3 of its errors until no mistake was made on 3 consecutive trials. Such positional corrections were counted towards the daily total of 30 trials.

Animals were also tested informally and formally for the presence of field defects. In the formal test 11 peanuts were placed in line on a black horizontal shelf (19 in. $\times$ 11 in.) set in front of the animal in the large wooden apparatus previously described. The animal was allowed to remove 3 nuts on each of 6 trials given on two different days. The position was recorded of each nut that the animal removed.

Sequence of operations and training.—Animals were allocated to a predetermined operative sequence at random. Details of the order and nature of the surgical procedures and of the training undertaken with each animal may be found in Table I. It will be seen that animals 1–6 learnt the discrimination preoperatively, whereas animals 7–12 had received 1 or 2 lesions before training began. The table also shows that every animal was required to relearn the discrimination after an interval of fourteen days' rest and before proceeding to the next operation whenever it had made more than 10 errors in the initial 100 trials of learning or post-operative re-learning. Up to three days elapsed between the end of a period of re-learning and the subsequent surgical intervention. No training was given on the pattern discrimination for a period of fourteen days following surgery. Informal charting of the visual fields was attempted by more than one observer during the first week after section of the left optic tract. The formal testing for field defects was carried out on the two days preceding surgery to the left optic tract and again between the tenth and thirteenth post-operative day.

Results

Gross Behaviour Changes

A variety of neurological disorders and behaviour changes were observed as a result of the brain lesions. Thus following surgery to the

left optic tract there was a partial or complete ptosis of the left eye in animals 1, 6 and 9, and the heads of animals 5 and 6 were permanently held tilted to the right. A persistent right hemiparesis of varying severity (but mostly appearing to affect the leg more severely than the arm) came on in the case of animals 1, 2, 4, 5 and 6 as a consequence of the operation for section of the left optic tract. The immediate visual effects of this operation were not the same for all animals. Animals 1, 2, 4, 6 and 8 appeared to be totally blind for up to twenty-four hours after recovery from the anæsthetic. In contrast the remaining animals responded to visual as soon as to tactile and auditory stimulation. However all animals gave evidence of a complete homonymous hemianopia to the right on informal testing a few days after section of the left optic tract. This finding received subsequent support from the results on the formal test for field defects. For all animals, excepting only numbers 7, 9 and 11, after surgery selected significantly more nuts from the left end of the row than would be expected by chance, whereas choice was more evenly distributed between left and right ends before surgery (binomial test). As regards the 3 exceptional animals, number 7 was thought to have a left upper quadrantic defect in addition to the right hemianopia.[1] Animal 11 continually sat in the front right-hand corner of the transport cage. Although it took nuts lying only to its own left, nevertheless these nuts formed part of the right end of the row owing to the animal's exceptional position.

For up to about five weeks following surgery most animals chose to make a three-quarter turn to the left rather than a quarter turn to the right when their attention was drawn in this direction. Moreover all animals that had previously used the right hand to take food without exception made use of the left following section of the left optic tract. In certain animals (numbers 2, 4, 5 and 6) the change from right to left hand preference could reasonably be attributed to the right hemiparesis. However no signs of paralysis were observed in animals 3, 7, 8, 9 and 11, and these likewise permanently changed their preference from right to left hand after section of the left optic tract.

In animals 4 and 12 the right optic tract was cut subsequent to section of the left tract to secure essential behavioural verification of the effectiveness of the earlier surgical procedure. Animal 4 was observed for twenty-four hours, animal 12 for forty-eight hours after section of the right tract. Although reactivity to auditory and tactile stimulation was regained after recovery from the anæsthetic and appeared to be intact neither animal ever again responded to visual stimulation. Moreover in both animals the pupillary light reflexes were absent in the two eyes throughout the period of observation. Animal 12 was able to walk

[1]The left optic tract was seen on histological examination to be cut further medially and in closer proximity to the chiasm in this animal than in the others.

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and climb well towards the end of the forty-eight hour survival period but failed to avoid obstacles.

Animal 9 suffered respiratory arrest and required artificial respiration during the operation for removal of the right frontal cortex. This animal was transiently blind (for about six hours) following surgery and persisted in circling to the left during the two-month period of survival. Such changes did not follow the larger frontal ablation in animal 7.

The operation for section of the corpus callosum was followed by a paralysis of the right leg and doubtful paralysis of the right arm in animal 3. No neurological changes were observed in animal 6 following a similar operation. However animal 8 became paralysed in the right leg on the third day after callosal section and developed frequent right-sided seizures on the fourth and fifth post-operative days, but not thereafter.

Pattern Discrimination

A summary of the findings on the pattern discrimination has been previously communicated elsewhere (Ettlinger, 1958). Full details of the number of trials required by every animal to achieve the standard level of performance at each stage of training are given in Table I.

Effect of single lesions on re-learning.—The range of the number of trials required to re-learn the discrimination following section of the left optic tract (animals 1–3) is 70–210. The range of the average number of errors per 100 trials of training ("average errors") is 21–26 for these 3 animals. In contrast animals 1–6 were all able to re-learn the discrimination in 0 trials (that is made 10 or less errors in the first 100 trials), with a range of average error of 0–3, when fourteen days had elapsed without surgical intervention. Therefore section of the left optic tract (animals 1–3) give rise to mild impairment in re-learning.

Animals 4–6 all re-learnt the discrimination in 0 trials following a unilateral temporal ablation (range of average errors being 0–8). Therefore a unilateral temporal lesion (animals 4–6) gives rise to no impairment in relearning according to the measure of the number of trials.

Statistical comparison[1] between the effects of section of the left optic tract and ablation of one temporal region indicates a significantly greater retardation in relearning the discrimination following the former lesion ($p = 0{\cdot}05$).

Effect of single lesions on initial learning.—Animals 7 and 8 required 1,050 and 440 trials to learn the discrimination for the first time after section of the left optic tract (average errors being 42 for both animals). In contrast animals 1–6 were able to learn the discrimination for the first

[1]The Mann-Whitney test was used in this and all subsequent statistical comparisons.

TABLE I

TABLE I

Sequence of training and of operations for all animals. In this and the following tables the figures refer to the number of trials in excess of 100 required to reach the standard level of performance (10 or less errors in 100 trials) on the pattern discrimination. The symbol + indicates that the animal failed to reach the standard level of performance within the stated number of trials. — indicates that re-learning was not undertaken at this stage. The larger spacing between procedures represents the interval of fourteen days' rest between either (re-) learning or operation and subsequent (re-) learning. L signifies left-sided; R, right-sided; Tr, optic tract; Tm, temporal; Call, callosal; Fr, frontal.

Animal	1	2	3	4	5	6	7	8	9	10	11	12
Learning	510	340	280	200	430	390						
Re-learning	0	0	0	0	0	0						
1st operation: ..	L. Tr	L. Tr	L. Tr	L. Tm	R. Tm	R. Tm	L. Tr	L. Tr	L. Tm	R. Tm	L. Tr L. Tm	L. Tr R. Tm
(Re-) learning ..	210	80	70	0	0	0	1,050	440	690	780	480	1,140
Re-learning	0	0	0	—	—	—	10	0	0	0	0	0
2nd operation: ..	L. Tm	R. Tm	Call	L. Tr	L. Tr	Call	L. Tm	R. Tm	L. Tr	L. Tr	R. Tm	L. Tm
Re-learning	0	220	0	0	1,250+	0	0	150	80	450	380	510
Re-learning	—	0	—	—		—	—	0	0	0	20	0
3rd operation	R. Tm	L. Tm	R. Tm			L. Tr	R. Fr	Call	R. Fr.	L. Tm		
Re-learning	1,250+	220	1,000+			1,250+	0	290	700	0		
Re-learning		0					—	0	20			
Subsequent operation:				R. Tr			R. Tm					R. Tr
Re-learning				Blind			840					Blind

time in 200–510 trials prior to any surgical intervention (range of average errors being 31–42). Despite the overlap of scores there is then a suggestion that section of the left optic tract (animals 7 and 8) may give rise to impairment in learning ($p=0{\cdot}07$).

Animals 9 and 10 required 690 and 780 trials to learn the discrimination following a unilateral temporal ablation (average errors being 45 and 43). Therefore a unilateral temporal lesion (animals 9 and 10) gives rise to impairment in learning ($p=0{\cdot}036$).

Effect of two lesions.—Animals 4 and 9 required 0 and 80 trials to relearn the discrimination when the left optic tract was cut subsequent to a left temporal ablation (average errors being 3 and 11). Therefore section of the left optic tract subsequent to a left temporal lesion (animals 4 and 9) gives rise to no greater impairment than does section of the left optic tract alone (animals 1–3). Animals 1 and 7 both required 0 trials to re-learn the discrimination when the left temporal region was ablated subsequent to section of the left optic tract (average errors being 9 and 2). Therefore ablation of the left temporal region subsequent to section of the left optic tract (animals 1 and 7) gives rise to no greater impairment according to the measure of the number of trials than does ablation of one temporal region alone (animals 4–6).

Combining these results for animals 1, 4, 7 and 9, successive lesions to the left optic tract and left temporal region in either order are seen to give rise to no greater impairment in re-learning the discrimination than can be expected to follow section of the left optic tract by itself. These results are shown in Table II.

TABLE II

Effect of successive section of the left optic tract and ablation of the left temporal region upon re-learning of the pattern discrimination

Animal	1	4	7	9
	Learning			
	Re-learning			
1st operation	L. tract	L. temp.	L. tract	L. temp.
	Re-learning		Learning	
			Re-learning	
2nd operation	L. temp.	L. tract	L. temp	L. tract
No. of trials to standard level of performance	0	0	0	80

Animal 5 required more than 1,250 trials and animal 10 required 450 trials to re-learn the discrimination when the left optic tract was cut subsequent to a right temporal ablation (average errors being 49 and 32). Therefore section of the left optic tract subsequent to a right temporal lesion (animals 5 and 10) gives rise to considerably greater impairment than does either section of the left optic tract alone (animals 1–3) or section of the left optic tract subsequent to a left temporal lesion

(animals 4 and 9). Animals 2 and 8 required 220 and 150 trials to re-learn the discrimination when the right temporal region was ablated subsequent to section of the left optic tract (average errors being 28 and 18). Therefore ablation of the right temporal region subsequent to section of the left optic tract (animals 2 and 8) gives rise to considerably greater impairment than does either a unilateral temporal ablation alone (animals 4–6) or a left temporal ablation subsequent to section of the left optic tract (animals 1 and 7).

Combining the results for animals 2, 5, 8 and 10 (*see* Table III), successive lesions to the left optic tract and right temporal region in either order are seen to give rise to significantly ($p=0{\cdot}014$) greater impairment in relearning the discrimination than do successive lesions to the left optic tract and left temporal region (animals 1, 4, 7 and 9 of Table II).

TABLE III

Effect of successive section of the left optic tract and ablation of the right temporal region upon re-learning of the pattern discrimination

Animal	2	5	8	10
	Learning			
	Re-learning			
1st operation	L. tract	R. temp	L. tract	R. temp
	Re-learning		Learning	
			Re-learning	
2nd operation	R. temp	L. tract	R. temp	L. tract
No. of trials to standard level of performance	220	1,250+	150	450

Only 2 animals (numbers 11 and 12) learnt the discrimination for the first time after a left or right temporal ablation had already been combined with section of the left optic tract. The score of 480 trials for animal 11 (both lesions on the same side of the brain) falls within the range of scores obtained from unoperated animals (numbers 1–6) in learning the discrimination. The score of 1,140 trials for animal 12 (lesions on opposite sides of the brain) exceeds the scores of all other animals for initial learning.

Animals 3 and 6 both relearnt the discrimination in 0 trials when the corpus callosum was cut subsequent to a left optic tract section (animal 3) or right temporal ablation (animal 6) (average errors being 4 and 0). These scores may be compared with those achieved by animals 1–6 in re-learning prior to surgical intervention. Therefore section of the corpus callosum subsequent to a tract or temporal lesion gives rise to no impairment in re-learning according to the measure of the number of trials.

Effect of further lesions.—As shown in Table IV, animals 1, 7 and 11 required from 380 to more than 1,250 trials to re-learn the discrimination

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when the right temporal region was ablated subsequent to both left optic tract and left temporal lesions (range of average errors being 33–51). Therefore ablation of the right temporal region subsequent to both left tract and left temporal lesions (animals 1, 7 and 11) would appear to give rise to greater impairment than does ablation of the same temporal region subsequent only to section of the left optic tract (animals 2 and 8, Table III).

TABLE IV

Effect of ablation of the right temporal region subsequent to both section of the left optic tract and ablation of the left temporal region upon re-learning of the pattern discrimination

Animal	1	7	11
Pre-existing lesions	L. tract L. temp	L. tract L. temp R. frontal	L. tract L. temp
Further ablation	———	R. temporal	———
No. of trials to standard level of performance	1,250+	840	380

As shown in Table V animals 2, 10 and 12 required from 0 to 510 trials to re-learn the discrimination when the left temporal region was ablated subsequent to both left optic tract and right temporal lesions (range of average errors being 10–22). Similarly animal 8 required 290 trials when the corpus callosum was cut subsequent to both left optic tract and right temporal lesions (average errors being 41). Therefore ablation of the left temporal region (animals 2, 10 and 12) or division of the callosum (animal 8) subsequent to both left tract and right temporal lesions would as a rule seem to give rise to greater impairment than can be expected to follow either ablation of the left temporal region (animals 1 and 7) or division of the callosum (animal 3) subsequent only to section of the left optic tract. On the other hand ablation of the left temporal region subsequent to both left tract and right temporal lesions (animals 2, 10 and 12, Table V) tends to give rise to less impairment than does ablation of the right temporal region subsequent to both left tract and left temporal lesions (animals 1, 7 and 11, Table IV).

TABLE V

Effect of ablation of the left temporal region or section of the corpus callosum subsequent to both section of the left optic tract and ablation of the right temporal region upon re-learning of the pattern discrimination

Animal	2	8	10	12
Pre-existing lesions	L. tract R. temp.	L. tract R. temp.	R. temp. L. tract	L. tract R. temp.
Further lesion	L. temp.	Callosal	L. temp.	L. temp.
No. of trials to standard level of performance	220	290	0	510

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As shown in Table VI, animal 3 failed to re-learn the discrimination within 1,000 trials when the right temporal region was ablated subsequent to both left optic tract and callosal sections (average errors being 40). Similarly animal 6 failed to re-learn the discrimination within 1,250 trials when the left optic tract was cut subsequent to both right temporal and callosal lesions (average errors being 40). Therefore the combination of left tract and right temporal lesions subsequent to callosal section (animals 3 and 6) gives rise in these animals to considerably greater impairment than does the combination of left tract and right temporal lesions alone (animals 2, 5, 8 and 10, Table III).

TABLE VI

Effect of the combination of section of the left optic tract and ablation of the right temporal region subsequent to division of the corpus callosum upon re-learning of the pattern discrimination

Animal	3	6
First lesion	L. tract	R. temporal
Second lesion	Callosal	Callosal
No. of trials to standard level of performance	0	0
Further lesion	R. temporal	L. tract
No. of trials to standard level of performance	1,000+	1,250+

Animals 7 and 9 required 0 and 700 trials to re-learn the discrimination when the right frontal cortex was ablated subsequent to both left optic tract and left temporal lesions (average errors being 6 and 40). Therefore ablation of the right frontal cortex subsequent to both left tract and left temporal lesions gives rise to performance that is either superior (animal 7) or much inferior (animal 9) than that which can be expected to follow ablation of the right temporal region subsequent to section of the left optic tract (animals 2 and 8).

DISCUSSION

It has been shown that monkeys rendered hemianopic by section of the left optic tract make more errors in re-learning the pattern discrimination than do unoperated control animals. Hemianopic monkeys also tend to be retarded by comparison with unoperated animals in learning the discrimination for the first time. Under both conditions of learning the degree of impairment is generally slight. As all animals had some damage, varying in extent and location, of the medial part of the globus pallidus and of some fibres of the internal capsule in association with the section of the left optic tract it is not possible to ascribe any ensuing impairment on the pattern discrimination exclusively to section of this tract. Nevertheless the extent of the unintentional damage in these two structures varied from one animal to another, as did also the occurrence

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of incidental damage in other structures in the neighbourhood of the left optic tract, without obvious correlation with the test performance. Similarly the degree of impairment subsequent to section of the left optic tract cannot be readily correlated with the presence or severity of a hemiparesis to the right. Nor yet was animal 1, which pre-operatively preferred the use of its left hand, less severely impaired than other animals which changed their preference from the right to the left hand following surgery. A similar alteration in hand preference favouring the hand on the side of the remaining intact visual half-field has been previously reported as a result of striate lesions in monkeys by Klüver (1937) and Settlage (1939). At any rate the majority of errors were made by the hemianopic animals when the positive cue was placed to the side of the blind right half-field. It would then seem reasonable to relate the deficit in these animals to a transient failure of visual searching towards the right. The animals had to learn to look actively for an alternative cue when the negative pattern was presented in the intact left half-field. This visual search was initially achieved by a three-quarter turn to the left, and only later by a head movement to the right.

The present results serve to confirm previous reports (e.g. Mishkin and Pribram) that a visual discrimination may be re-learnt in as few trials after a period allowed for recovery from a unilateral infero-temporal ablation as after an equal interval without surgical intervention. However, initial learning of the pattern discrimination was shown to be retarded after ablation of either the left or right temporal region. This finding accords with other evidence (Mishkin and Hall) that bilateral temporal lesions give rise to greater impairment when a discrimination is learnt for the first time following surgery than when it is first learnt before and then re-learnt after the lesions are made. Therefore re-learning is more obviously disrupted than is initial learning by section of one optic tract whereas the converse result is the rule after a unilateral temporal ablation. Such contrasting effects of the two kinds of lesion provide some measure of support for the findings of Wilson and Mishkin, who compared the behaviour of animals with striate and temporal ablations and also reported a dissociation in the effects of the lesions.

It is of some interest that a unilateral temporal ablation consistently gives rise to defective re-learning of the pattern discrimination when it is placed on the side of the brain opposite to a section of the optic tract, but fails to do so when these two lesions are both placed on the same side of the brain. There is no overlap between the scores of animals with left tract and right temporal lesions on the one hand, and of animals with left tract and left temporal lesions on the other. It might be claimed that the deficit of the former group is the result of non-specific interaction between lesions on opposite sides of the brain, and not primarily the result of temporal involvement. This possibility cannot be entirely

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rejected on the present findings. Two lines of evidence would, however, tend to contra-indicate such an argument. Firstly, combined left tract and right frontal lesions (in addition to left temporal ablations) give rise to either smaller (animal 7) or to greater (animal 9)[1] impairment than do combined left tract and right temporal lesions. Secondly, the combination of left tract and right temporal lesions subsequent to division of the corpus callosum disrupts re-learning of the discrimination at least as severely as does the ablation of both left and right temporal regions.

It would then appear from these results that there is a preferential relationship between a given infero-temporal region and behaviour dependent upon the primary visual inflow to the *same* hemisphere (or, if the assumption is made that each temporal region ultimately interacts with the visual inflow or its derivations during visual discrimination, then each temporal region would appear to interact preferentially with the inflow or its derivatives arriving in the *same* hemisphere). For if, say, the left temporal region were as intimately related to behaviour dependent upon the visual inflow to the right as to behaviour dependent upon the visual inflow to the left hemisphere, then a left temporal ablation would be expected to disrupt visual discrimination as severely as a right temporal ablation when the visual inflow is restricted (by section of the left optic tract) to the right hemisphere. The present evidence would then suggest that the disorder of visual discrimination consequent upon bilateral temporal lesions in monkeys does not occur at so high a level of visual perception as to be quite independent of laterality.

However, it had been originally predicted (on the assumption that ablation of each temporal region gives rise to a qualitative change in visual efficiency in the contralateral half visual field) that combined lesions to the left optic tract and right temporal regions would impair visual discrimination as severely as combined left and right temporal ablations. Animals with left tract and left temporal lesions were therefore subjected to ablation of the right infero-temporal region. More trials were then required by all of these animals to re-learn the discrimination than by other animals which had the right temporal region ablated subsequent only to section of the left optic tract. The inference would therefore seem inescapable that preservation of the left temporal region minimizes the impairment consequent upon combined left tract and right temporal lesions.

An extension of this inference is legitimate on the basis of the further finding that 2 out of 3 animals were impaired when the left temporal region was ablated subsequent to both left tract and right temporal lesions (animals 2 and 12). This result runs contrary to any interpreta-

[1]As already reported above animal 9 may have become severely anoxic during the operation for removal of the right frontal cortex.

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tion of the visual disorder in temporal monkeys as being secondary to damage to any part of the primary visual afferent system. For the visual deficit ensued in these two animals as a consequence of a temporal lesion to a hemisphere in which the visual afferent system had already been totally inactivated by section of the optic tract. Behavioural verification of the total blockage of visual afferents to the left hemisphere was forthcoming in the case of animal 12 (which suffered the greater visual deficit). For it was rendered completely blind by eventual section of the right optic tract. It would therefore seem to be the case that, *provided the opposite temporal region has previously been destroyed*, each infero-temporal region can become concerned in behaviour dependent upon the visual inflow to the opposite hemisphere. Such a relationship so to speak "across the brain" would not, however, appear to be ever as effective as is that within one hemisphere (compare Tables IV and V).

The connecting pathways by means of which each infero-temporal region might ultimately interact with the visual inflow or its derivatives in discrimination learning are not known. Collicular, thalamic and direct occipito-temporal cortical circuits have all been rejected on experimental evidence. Some information on this point could be gained in the present study. In monkeys with combined left tract and right temporal lesions no visual inflow (primary or derivative) is known to reach the left hemisphere except from the right striate area through the corpus callosum. Bremer and Stoupel (1956) have obtained electrophysiological evidence for the interaction of the two striate areas by this route on stimulation of one lateral geniculate body. Division of the corpus callosum would then serve to abolish all known visual inflow to the left hemisphere. As a result even those extra-temporal regions of the left hemisphere which, with homologous areas on the right, must be assumed to take over the functions of the temporal sector after bilateral temporal ablations, would be isolated. Total section of the corpus callosum in combination with appropriate other lesions as shown in Tables V and VI[1] does in fact afford support for the view that the left temporal region is dependent upon visual messages that pass from the right to the left striate area through the corpus callosum after destruction of the right temporal region. Further pathways between the left striate and temporal regions may then be presumed to exist, even though perhaps involving multiple synapses. It would seem reasonable to suppose that these same occipito-temporal pathways are in use when visual inflow arrives at each striate area directly in the intact animal. However it

[1]The severity of the impairment resulting from combined left tract and right temporal lesions subsequent to section of the callosum is especially noteworthy; it is thought to follow from isolation of both temporal and extra-temporal areas of the left hemisphere. In contrast animal 8 of Table V had been impaired following the first two lesions, so that the right extra-temporal region may have already assumed temporal functions before the callosal section.

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cannot be claimed with certainty on the basis of the present results that the corpus callosum is concerned with visual discrimination in the intact monkey.

Some further implications follow from the present results. Firstly, successive variation of the neurological status of the animal by means of serial lesions under constant conditions of behavioural observation has been shown to be of value in the analysis of behaviour changes resulting from brain lesions (cf. also Chow and Survis, 1958). This method is, however, merely complementary to other procedures in which test conditions are systematically varied in conjunction with only one change in neurological status. Secondly it would appear that the action of that region within the "association cortex" of the monkey known to be concerned with visual performance has been delimited somewhat more clearly. For this region has been shown to influence visual discrimination not by direct interaction at any level with the geniculo-striate afferent system. Rather, it would seem to be concerned with visual messages proceeding from the striate areas, and in such a way that the temporal region on each side of the brain is predominantly, but not invariably, related to the messages leaving the striate area of the same hemisphere.

The recent findings of Mishkin (1958) who has combined unilateral temporal ablations with striate removals in the same and opposite hemisphere and with section of the corpus callosum, although as yet only reported in abstract afford confirmation of many of the results presented in this paper.

Summary

The behavioural manifestations of a visual disorder that follows bilateral inferior temporal lesions in the monkey are described, and their relevance to perceptual disturbances in man are discussed. It is argued that the possible contribution of areas of amblyopia in the genesis of this disorder in monkeys has not been adequately examined.

An investigation of the effects of various successive lesions on the ability to learn and retain a visual pattern discrimination was undertaken in 12 monkeys. The findings suggest that in the monkey the infero-temporal regions influence visual discrimination behaviour not by direct interaction at any level with the primary visual afferent system, but rather by interaction with messages proceeding *from* the striate areas. It has also been shown that each infero-temporal sector is preferentially related to behaviour dependent upon the primary visual inflow to the *same* hemisphere, although a given sector may interact with messages proceeding from the opposite striate area via the corpus callosum provided that the opposite temporal area has previously been ablated.

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CHANGES IN VISUALLY GUIDED BEHAVIOUR FOLLOWING MIDSAGITTAL DIVISION OF OPTIC CHIASM AND CORPUS CALLOSUM IN MONKEY (*MACACA MULATTA*)[1]

BY

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INTRODUCTION

SECTIONING the optic chiasm in the midsagittal plane in mammals restricts the afferent connections from each eye to its ipsilateral hemisphere. When an animal, prepared in this manner, has been trained to choose consistently one of a pair of visual stimulus-objects with one eye open, it has been shown that the animal retains the habit when the open eye is closed and the formerly closed eye is opened (Myers, 1955). When the optic chiasm and the corpus callosum both have been sectioned, transfer of monocularly learned visual discrimination habits in cat (Myers, 1956) and monkey (Downer, 1958) does not occur. This latter study showed that transfer of colour and form discrimination habits occurred when either the optic chiasm or corpus callosum had been sectioned but not when both had been sectioned.

Incidental to these investigations in the monkey, observations were made and a record kept as to which hand each animal used to pick up the stimulus-objects. This was done to determine, first, whether or not there were any signs suggesting dominance of either cerebral hemisphere, and second, whether or not there would be a shift in the hand used in visually guided tasks, depending upon which eye was open, following midsagittal division of both optic chiasm and corpus callosum. With the optic chiasm and corpus callosum both sectioned, and with one eye open, the total visual input would be restricted to the cerebral hemisphere receiving afferent fibres from the open eye. In terms of motor representation, this

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hemisphere has predominant control over the opposite side of the body. It might, therefore, be supposed that visually guided movements initiated by the cerebral cortex of the hemisphere receiving the visual input would be limited to the contralateral musculature since following transection of the corpus callosum all intercortical connexions between the visual areas of the one hemisphere and the motor cortex of the other hemisphere would have been severed.

Methods

Six monkeys (*Macaca mulatta*) were observed. At the beginning of experimentation they each weighed approximately 3·5 kg. All surgical procedures were performed under general anæsthesia (30 mg. sodium pentobarbital/kg. body weight).

Prior to testing, each animal had one eye closed by trimming away the borders of the eyelid, approximating the trimmed margins and suturing them together. When it became necessary to open the eye, the point of a pair of scissors was forced through the adhered tissue along the palpebral line and a cut was made from the lateral palpebral ligament to the lacrimal canaliculus. At this time the other eye was closed. A period of three to four days was allowed before testing was continued.

The optic chiasm was sectioned in the midsagittal plane via a trans-buccal approach. The animal was placed in the supine position with its head dorsiflexed. The trachea was intubated with a small calibre tube. The mouth was thoroughly washed with a solution of isotonic saline followed by Zephiran (1 : 5,000). The animal was draped as with aseptic technique. A "U"-shaped incision was made through the soft palate into the nasopharynx. This incision began laterally and caudally just anterior to the isthmus of the fauces and was carried rostrally to about 2 mm. over the caudal margin of the bony palate, then crossed to the other side and was carried caudally to the same level from which it had begun. The underlying membranous septum was severed and the flap thus formed was reflected from the field. The spinous process of the vomer was trephined away. The mucosa overlying the vomer and sphenoid bones was scraped away and the entire nasopharynx and buccal cavity filled with Zephiran (1 : 5,000) for approximately fifteen minutes. From this stage on all instruments placed in the surgical field were first "flamed" in an attempt to keep the field sterile. A dental burr was placed on the suture separating the sphenoid bone from the vomer and a hole was drilled through into the cranial cavity. The hole was enlarged anteriorly until the optic nerves could be seen joining to form the optic chiasm, and posteriorly until the anterior hypophysis was clearly exposed. Under a binocular dissecting microscope the optic chiasm was sectioned longitudinally in the mid-line. A small square of artificial dura (polyethylene) was placed over the optic chiasm and tucked under the edges of the hole. A fast-curing liquid plastic was poured into the hole. This set within a few minutes to form a hard, bone-like plug. The cut edges of the palate were approximated and closed with interrupted sutures of fine silk and a continuous plain cat-gut suture. 400,000 I.U. penicillin and 0·3 gramme of chloromycetin were administered daily for ten days. Two weeks were allowed for recovery before testing began.

After one eye had been closed and the optic chiasm sectioned, each animal was placed in turn in the training apparatus. This consisted of two compartments separated from one another by a sliding door. The animal was placed in one compartment, the stimulus-objects in the other. When the door was raised the animal was confronted by two different visual stimulus-objects. Each of these was mounted upon a cup. A reward (raisin) was placed under the cup of the positive (correct) stimulus-object. No punishment was introduced for choosing the negative (incorrect) stimulus-object. A "trial" consisted of raising the door, giving the animal access to the

stimulus-objects. The "correction" technique was used during the first 60 trials; that is, if the animal first chose the negative stimulus-object the door was kept open until it had moved over and picked up the positive stimulus-object and obtained a raisin. Thereafter, "non-correction" procedure was adopted; the animal was given only one choice; if this was incorrect the door was lowered and the animal was not rewarded. The stimulus-objects were randomly varied from side to side at each presentation to prevent positioning cues. Thirty trials a day were given until the animal reached an arbitrarily set criterion of 90 per cent correct choices on two successive days. Upon reaching criterion the closed eye was opened, the open eye closed, and the animal reintroduced to the apparatus and tested for its ability to continue choosing the correct stimulus-object. Owing to the exigencies of the experiment in interhemispheric transfer of training, three of the animals of this group were not observed at this time with their left eyes closed and one was not observed with its right eye closed.

The corpus callosum was transected via a large left fronto-parieto-occipital osteoplastic craniotomy. The bone flap was hinged on the left temporal muscle. The opening extended to 1–2 mm. of the mid-line. The dura was incised longitudinally and reflected medially and laterally. It was sometimes necessary to ligate and section one of the superior anastomotic veins at its entry to the sagittal sinus The left hemisphere was then gently retracted from the falx and the entire dorsal surface of the corpus callosum brought into view. This structure was sectioned throughout its length with a small spatula, care being taken not to tear any of the branches of the anterior cerebral artery. The wound was closed in the usual manner. Each animal received 100,000 I.U. penicillin daily for seven days. Two weeks were allowed for recovery before testing was resumed.

The testing and training procedure here was essentially the same as before. The animals were retested, using each eye in turn, on all previously learned visual discriminations; then trained and tested, again using each eye in turn, on a series of new visual discrimination problems. During all these trials, both fore-limbs were unhampered so that the animals had a free choice of which hand to use. At the conclusion of the experiments, each fore-limb in turn was restrained by a wrist strap fastened to a belt secured about the animal's waist. With the right fore-limb restrained the animal's performance was observed first with its right eye open and then with its left eye open. The same procedure was used with the left forelimb restrained.

Results

Because of the variable number of trials each animal received in the training and testing situation, the absolute scores have been reduced to percentage scores for easier comparison. These scores together with the total number of trials are listed in Table I and represented graphically in fig. 1.

Following transection of the optic chiasm no significant change in hand preference occurred irrespective of which eye was open, nor was there any demonstrable relationship between the open eye and the hand used. D-22 was moderately right-handed with either eye open. D-24 was markedly right handed with its left eye open and remained so with the right eye open. With the left eye open both D-26 and D-29 were markedly left handed while D-27 was markedly right handed. With the right eye open D-17 was left handed.

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TABLE I.—THE HAND USED IN PICKING UP THE STIMULUS-OBJECTS IS SHOWN AS A PER CENT SCORE. THE TOTAL NUMBER OF TRIALS WHICH EACH ANIMAL RECEIVED UNDER EACH CONDITION IS SHOWN IN PARENTHESIS

	Optic chiasm sectioned in midsagittal plane		*Corpus callosum transected*	
Animal No.	*Left eye open*	*Right eye open*	*Left eye open*	*Right eye open*
D-17				
Left hand	—	88·6	2·5	97·4
Right hand	—	11·4	97·5	2·6
		(585)	(552)	(370)
D-22				
Left hand	38·1	43·8	6·4	96·8
Right hand	61·9	56·2	93·6	3·2
	(370)	(419)	(480)	(670)
D-24				
Left hand	4·7	6·4	7·3	97·3
Right hand	95·3	93·6	92·7	2·7
	(480)	(481)	(476)	(359)
D-26				
Left hand	96·1	—	20·0	100·0
Right hand	3·9	—	80·0	0·0
	(490)		(454)	(620)
D-27				
Left hand	4·0	—	0·0	90·8
Right hand	96·0	—	100·0	9·2
	(401)		(60)	(120)
D-29				
Left hand	99·5	—	27·5	100·0
Right hand	0·5	—	72·5	0·0
	(40)		(403)	(360)

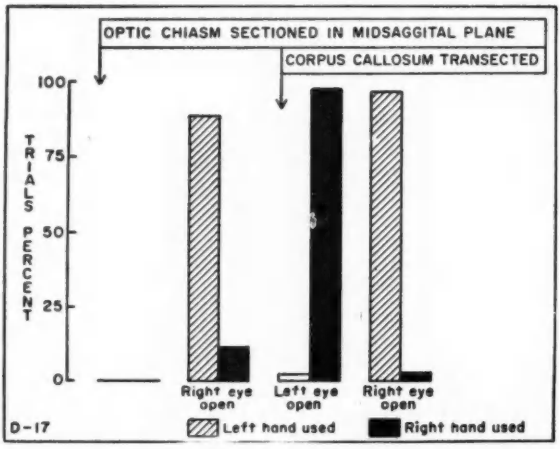

FIG. 1A.—Animal D-17

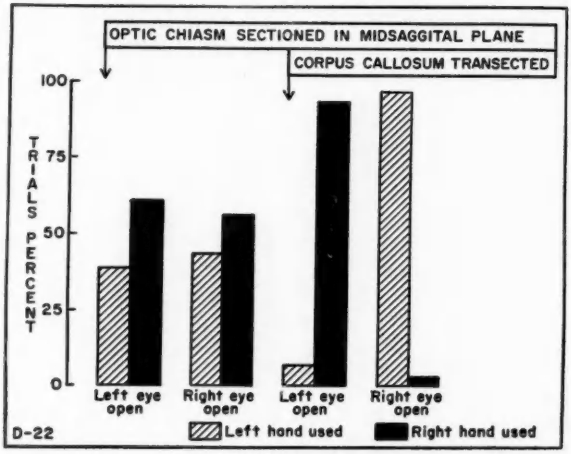

FIG. 1B.—Animal D-22

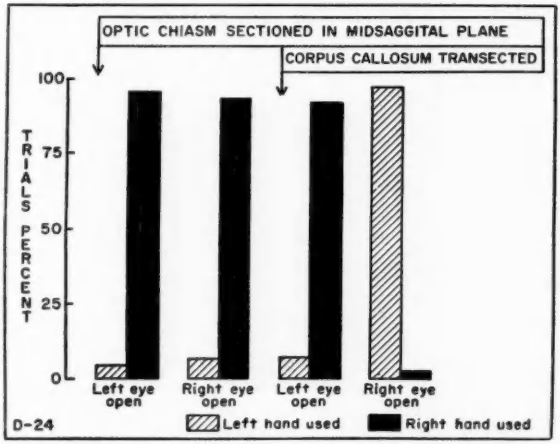

FIG. 1C.—Animal D-24

Following transection of the corpus callosum these relationships changed abruptly. With the left eye open all animals exhibited a strong right hand preference, ranging from 72·5 per cent to 100 per cent of the time. Closing the left eye and opening the right eye resulted in a sudden shift to the left hand; the scores ranging from 90·8 per cent to 100 per cent of the time. Although the animals occasionally picked up the stimulus-objects with the hand ipsilateral to the hemisphere receiving the visual input, it did not appear as if they were directing the hand by visual cues

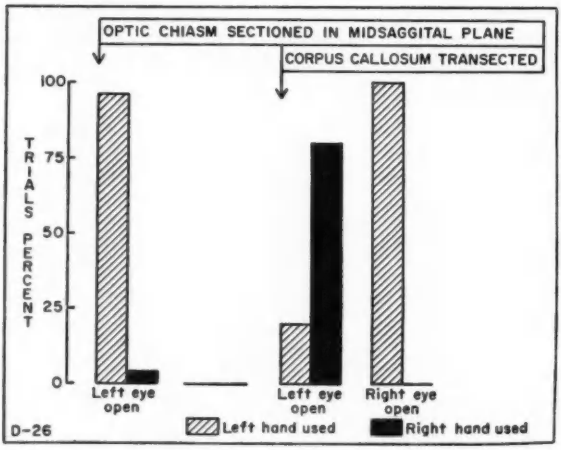

FIG. 1D.—Animal D-26

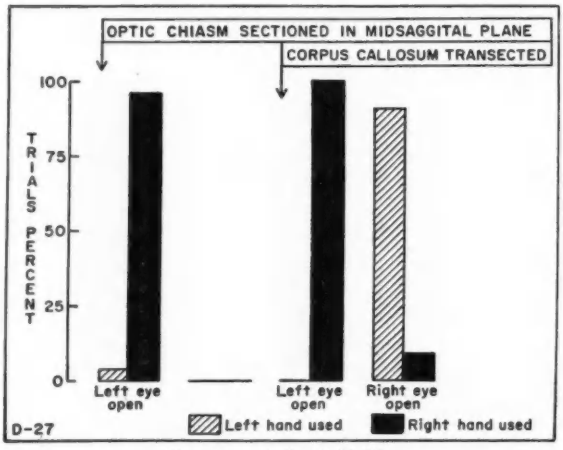

FIG. 1E.—Animal D-27

alone, *videlicit:* the animals would orient themselves in front of one of the stimulus-objects, extend the ipsilateral hand through the bars and then begin pawing and groping until (it seemed by accident) the cup was grasped. Frequently an animal would have its head turned aside during this manœuvre. On other occasions an animal would extend its contralateral hand to within close proximity of the cup. The ipsilateral hand would then slide down the contralateral arm and grasp the cup, as though the contralateral arm was being used as a guide for the ipsilateral hand.

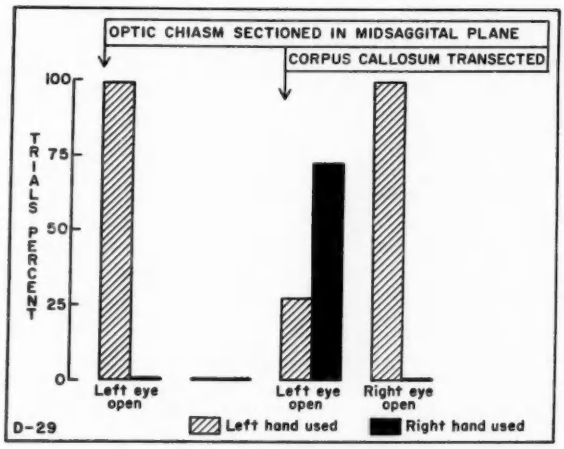

FIG. 1 F. — Animal D-29

FIG. 1.—The hand used in picking up the stimulus-objects is shown in trials per cent. The solid column represents the right hand and the hatched column represents the left hand.

Apart from the initial orientation in front of one of the stimulus-objects during each trial, the hand movements in these instances where the ipsilateral hand was used were similar to those that might be expected if the animals were blind. This persistence in using the ipsilateral hand occurred for only a brief time and then primarily when the ipsilateral hand was the normally preferred one.

With the right fore-limb restrained, and with the right eye open, movements with the left hand were sure, swift and deft. When the left eye was opened and the right eye closed, and with the same limb restrained, the movements were clumsy and awkward with much pawing and groping until the cup was found. This behaviour was immediately reversed when the right eye was again opened and the left eye closed. The same sequence of events occurred if one eye was kept open and the restraining strap changed from one limb to the other. For example, with the right eye open and the left fore-limb restrained, movements of the right hand were much less effectual than in the case where the right fore-limb was restrained and the left one free. It later appeared, however, that if the hand contralateral to the open eye was restrained for a sufficient length of time and testing carried out so that the animal could use only its ipsilateral hand, the movements became surer and swifter with much less fumbling. Although this general improvement occurred in all animals, their proficiency never quite reached the level attained when the other eye was open. It appeared at this time as if some visual control was acquired over the ipsilateral hand.

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Discussion

These observations on visually guided movements are in many respects similar to the results obtained in the transfer of training experiments. Merely restricting the sensory input to one cerebral hemisphere does not limit the effect derived from this input to that hemisphere alone when the commissural systems are intact. Furthermore, as there was no consistent relationship between the open eye and the hand used immediately following sectioning of the optic chiasm, it can be concluded that the behaviour was unaffected by the bitemporal hemianopsia consequent to the lesion. These considerations suggest that when a visual motor task is being performed monocularly, following division of the optic chiasm, visual guidance may be exerted over either hand. If the task is being performed where there is a preference for the hand contralateral to the hemisphere receiving the visual input, visual control over this hand originates in the same hemisphere receiving the visual input. Visual guidance with this hand implies that there is a functional link between the visual areas and the motor area of the same hemisphere. In this case transection of the corpus callosum has no effect and the animal can continue without difficulty in using the preferred (contralateral) hand. If instead, the other eye is used alone, and, as indicated, there is no change in hand preference, it immediately suggests that the hemisphere which is now receiving the visual input commands the motor response originating in the opposite hemisphere via the corpus callosum. In this latter case, transection of the corpus callosum blocks this command, and the animal must now switch to the unpreferred hand, controlled by the hemisphere receiving the visual input, or must use non-visual cues if performance with the preferred hand is to be continued.

Although no observations on hand preference were made on animals in which it was definitely known that only the corpus callosum was transected, previous investigators have concluded that transection of the corpus callosum in man produces no changes in handedness (Smith and Akelaitis, 1942). There is no argument here with such findings. Changes in handedness, as observed in these monkeys, are not thought to be related to cerebral dominance but to the inability of the animals to guide their hands by visual cues alone.

Two systems may be considered as operating together under normal conditions. In the one instance the afferent fibres from each eye ultimately discharge into both cerebral hemispheres; bilateral effector control could, therefore, be accomplished in the absence of the corpus callosum. On the other hand, where the optic chiasm only has been sectioned, bilateral effector control could be accomplished, first, by the motor system originating in the hemisphere receiving the visual input, and second, via intercortical fibres to the opposite hemisphere. Visually guided behaviour is blocked only if the optic chiasm and the corpus callosum are both sectioned.

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With prolonged practice it became apparent that when the animals were restrained from using the contralateral hand some visual control was acquired over the ipsilateral hand. This immediately raises the question as to whether or not this control was mediated by some ipsilateral effector system, possibly the uncrossed pyramidal tract. The time course for this development and the continual awkwardness of movement were in many respects similar to that seen in the recovery of function following ablation of the pre-central gyrus.

Summary

Observations made on hand preference in 6 monkeys revealed that when both the optic chiasm and corpus callosum had been sectioned, the hand used in visually guided movements became a function of which eye was open. The hand used in these instances was contralateral with respect to the cerebral hemisphere receiving the visual input. This condition was not thought to be obligatory unless the task demanded visual control over the hand. When the contralateral fore-limb was restrained, it appeared that with prolonged practice some visual control was acquired over the ipsilateral hand. The time course for this development and the awkwardness of movement suggested that this control was mediated by some ipsilateral effector system.

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INTELLIGENCE, BRAIN FUNCTION AND THE THEORY OF MIND[1]

BY

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IT is the amiable custom of memorial lecturers, in their introductions, to lug in the one memorialized, give him a pat or two on the back, and then dismiss him before getting down to serious business. Here I depart from custom, for John Hughlings Jackson is directly concerned in what I have to say. My subject today is the influence of neurology, and related neurophysiological work, upon the current development of psychological ideas: particularly ideas about intelligence, but also some more general ones concerning the nature of mind. The Montreal Neurological Institute, I have reason to know, has had a large share of such influence; and I have also reason to believe that this, in turn, is related to a constant harking back to Jacksonian precepts and practice. Hughlings Jackson's role in this amphitheatre has been something more than that of patron saint.

My first acquaintance with his work was here, twenty-one years ago, in circumstances which have determined much of my subsequent thought and research. There was a great deal for me to learn concerning the complications of brain damage in man, if the results were to be applied to psychological problems; and I must publicly record my indebtedness to the Fellows in 1937 and 1938 who, having found someone who knew less than they did, proceeded to take my education vigorously in hand. The situation here was unique; I do not know where else a psychologist could have found such training, nor such stimulation to research. If Jackson's name was invoked ritually, as it seemed at the time, I perceive in retrospect that the ritual had something to do with the stimulation. Elsewhere, psychologists *en masse* were avoiding the problem of consciousness and the relation of higher mental processes to specific brain functions; here there was no possibility of escaping it, and part of the reason is that Jackson did not hesitate to talk about mind in the same context as brain.

This problem is what we are to discuss this afternoon, and I shall begin

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historically. The advances of the past quarter-century have been extraordinarily great; the result today is a great welter of data in which order is hard to find; and some retracing of our path may help in gaining perspective, and so help in the planning of research.

Now it may seem that to speak of the events of only twenty-five or thirty years ago as "historical" is an abuse of language. To some of us, 1930 is the immediate past; but those of us who feel so must remember that to others here the twenties and thirties are antediluvian. And they may be right, scientifically. The criterion of what is historical, what modern, must be the extent to which thought has developed and changed. It is not merely that we know more about the brain and its functions in behaviour; our conceptions have changed fundamentally, our methods of study would hardly be recognized by the neurophysiologist or psychologist of 1925 and, though we are still working on the same problems if these are broadly defined, we hardly see them in the same light.

We need only go back to 1928, thirty years ago, to find Berger's discovery of the EEG. It is a far cry to Li and Jasper's (1953) study of the relation of single-neuron firing to the ECG; or a far cry from Sherrington's (1925) somewhat uncertain postulate of a "central inhibitory state" to Eccles' (1953) direct demonstration of the increased membrane potential that constitutes inhibition. It was an important point in the early thirties to show, for the first time, that there is self-maintained neural activity (i.e. without continued input to the system) as Adrian (1934) and his fellow-workers were doing, while Lorente de Nó (1933) was having to argue on anatomical grounds that closed pathways *must* be important in central neural function. It was possible as late as 1931 for psychologists to argue that mammalian spinal reflexes may be the product of pre- or post-natal conditioning: I know, for I was one of them, and though in view of my inexperience this does not mean much it may be added that an eminent physiologist knew of no evidence to rule the idea out. It was just about then in fact that Weiss (1936) was providing a new kind of evidence, with amphibian limb transplants, to show that reflexes are established without conditioning and not subject to change by conditioning.

Again, apart from uncinate fits no one seemed to have heard of the temporal lobe twenty years ago, either in man or in monkey; remember that Klüver and Bucy's report appeared only in 1939. Everything important and distinctive about man as a species was still being attributed to the frontal lobes. It was as recently as 1935 that the first modern descriptive account of aphasia was given by Weisenburg and McBride, adequately quantitative and with normal control data; even so, the lack of certainty about locus (including the question of lateral dominance), and lack of any clue concerning mechanisms—for example, in the distinction between hypofunction and dysfunction—becomes very marked when their work is set beside that of Robb (1948) and Roberts (1955).

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Such considerations make it not unreasonable to speak of the twenties and thirties as part of the historical period. Knowledge and thought have developed more than one might think, until one looks again at the earlier literature. When the pace is so rapid perspective is easily lost; and I hope that retracing two lines in our current development will allow us to see better where we stand today. The first of these topics is the relation of cortex to intelligence (or intellectual function), the second the non-specific function of the brain-stem in behaviour: its integrating and organizing role apart from sensory or motor transmission. If thereafter I become philosophical, it is not because philosophizing allows one to sound weighty while saying little, but because preconceptions about the theory of knowledge and the nature of mind can be, and still often are, stumbling-blocks in the way of scientific development.

Higher Functions of the Cortex

In the twenties the work of Cushing and of Dandy had already made it possible to remove large sectors of the human cortex without unreasonable risk, and by 1930 such operations were commonplace. They appeared to provide a new and decisive kind of evidence concerning localization of function, and a number of papers began to appear, mostly emphasizing the frontal lobe.

One reason for this emphasis was a long-standing preconception: that the frontal lobe is morphologically the distinctive feature of the higher brain (a proposition for which, it seems, the evidence is doubtful at best). But the main reason was that the largest removals were being made from the frontal lobe; a tumour can get bigger there before producing symptoms that take the patient to his doctor, and the prefrontal region is a sort of peninsula of the brain where the surgeon can hack away with relative safety.

With rare exceptions the cases being reported from other clinics at the time were cases of tumour removal. The Fellows in charge of my education would not let me draw conclusions from expanding lesions, however, but made me concentrate on scar removals. This was for a very good reason: the tumour case is of little value for the localization of function. Brain-operation cases were being reported in such numbers because the surgical lesion, supposedly, lets one know just what tissue is destroyed; whereas a pathological lesion is diffuse and ill-defined. But in fact a brain operation for tumour leaves not only the surgical lesion but also diffuse effects of pressure from the earlier growth of the tumour, often with dysfunction that is clearly revealed by the EEG. Defects of behaviour following such an operation cannot be ascribed to the surgical removal alone, and thus the localization of function that was being reported from other clinics had little validity.

But such reasoning carried no weight with my colleagues elsewhere, who

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were reporting positive results in their frontal-lobe studies and who were politely sceptical of the negative results I was obtaining at this Institute. Let me remind you of what these results were, briefly. After removal of his left prefrontal lobe by Dr. William Cone, a young man proceeded to make a perfect Stanford-Binet score (the Wechsler-Bellevue did not appear until 1939) and comparable scores on all the other intelligence tests, verbal or nonverbal, that I could give him (Hebb, 1939). Not one person in a thousand—or ten thousand—could have done as well, brain operation or no. This was at a time when everyone (except Jefferson, 1937) seemed convinced that loss of a prefrontal lobe should produce something approaching imbecility. The other outstanding case was the removal by Dr. Penfield of both prefrontal lobes in a young man who before operation had frequent fits, with intermittent psychotic behaviour and severe intellectual impairment; and who after operation was indistinguishable from normal, with an IQ of about 95, well within the "normal" range of 90 to 110 (Hebb and Penfield, 1940), despite the loss of somewhere around 15 per cent by weight of the total mass of the cerebrum.

These and other cases made it plain that the relation of intelligence to the brain was a far greater problem than anyone had suspected. They showed that the defects being reported in tumour cases, and ascribed to simple loss of frontal-lobe tissue, were in fact produced by pathological processes in the tissue that remained after operation, as Jefferson first proposed. About this time also, Rowe (1937) reported the first psychometric data following a right hemidecortication—his patient, incredibly, succeeded with tasks that would baffle 80 to 85 per cent of the normal population—making it certain beyond question that a new base of operations was needed for study of the relation of brain to intelligence. The data, taken as a whole, disposed of both the localization current at the time, with its emphasis on the frontal lobe, and of Lashley's principle of mass action, which was the main alternative approach.

The failure of the mass-action idea, in the lack of effect of large cortical removals on important aspects of general intelligence, was very disconcerting. At the time I was prepared to find no gross topographical separation of higher functions in the cortex, other than those of speech; I would not have been surprised if the theoretical basis of the mass-action idea needed some modification, but did take for granted that as a working principle, an empirical statement of relations, the mass-action idea would hold. All my research was planned on this basis, and it was disconcerting to say the least to find no effect of large injuries to the frontal lobe. It took some time to realize that such "negative" results might be more significant, researchwise, than what was planned in the first place.

By now, in 1958, the mass-action idea is clearly insufficient as a general principle, not only for man and the primates but also for the rat. In man and monkey it is now evident from a number of studies (cf. Teuber and

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Weinstein, 1954, p. 178) that anterior and posterior lesions of equal size are not similar in their effects, as mass action would imply; and also clear that right- and left-sided lesions in the human brain do not have similar effects, even apart from speech. This was a tentative conclusion of Weisenburg and McBride's; it is confirmed by McFie, Piercy and Zangwill (1950), and especially by Brenda Milner (1954) in showing a different quantitative pattern in the intelligence-test scores of right- and left-temporal-lobe patients. In the rat, Lansdell (1953) and Smith (1959) have shown that posterior cortex is more important for a generalized maze function than anterior cortex (if the rats are reared in a "free environment"; the very puzzling results also indicate that this is not true if the rats are reared in the restriction of the usual small cages). Obviously, the demonstration by Penfield and Rasmussen (1950) of hallucinatory activity aroused by stimulation of the temporal lobe, and nowhere else, supports the same conclusion. The interpretation of the temporal-lobe "memories" is still a problem, and the phenomenon is not of course concerned directly with the question of intelligence; but it does show that the temporal lobe has distinctive properties, and thus is opposed to any theory that implies equipotentiality of cortical function.

The need of an explanation for the extraordinary facts I met in this Institute, the intellectual status of patients following large scar removals but with the remaining brain tissue in good condition, stayed with me as a nagging problem after I had left. A hint of a possible solution was the apparent difference in the effects of early and late brain injury. This suggested the idea that conceptual development, once complete, might not be readily reversible (that intelligence might, as it were, have a certain inertia) and the idea that a large mass of tissue such as the frontal lobe might be necessary for the development of intellectual capacity but not necessary for its subsequent functioning. A number of facts supported the notion, which was published later (Hebb, 1942). It clarified some of the effects of birth injury, which differ in general pattern from the effects of injury at maturity, and provided a new approach to the problems of the decline of intelligence in the advanced years beyond 25, when brain degeneration has begun.

But the old-age problem as such is incidental. What is relevant is that the intellectual status of some of these patients suggested, or compelled, taking a new point of view concerning the nature of intelligence itself. The psychological literature of the time implied (and I took for granted) that "intelligence" is equivalent to "goodness of brain," anatomically and physiologically. The IQ, one might say, was considered to be a measure of raw, naked, unmodified brain power. This is the view that the brain-operation data, and the available data concerning the effect of birth-injury, brought into question. The alternative view was that experience must play a major role in developing conceptual activities, and that an

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intelligence test essentially samples these activities, not the physiological adequacy of the brain.

When the psychological evidence was examined from this point of view it seemed clearly confirmatory, and a better picture both of the nature of intelligence, and of the meaning of an intelligence-test score, began to emerge. Without going into all the evidence, let me just say that we must distinguish between (1) having a good brain, with the potential for intellectual development, and (2) the development itself. It seems that the action of the environment is to establish conceptual activities, and that these pyramid on themselves; the individual who develops concepts *A* and *B* then becomes capable of developing concept *C*—but not before. The peak of intelligence-test performance is reached somewhere about the age of 15, and the brain begins its course of slow degeneration about ten years later; but the pyramiding, the development of conceptual processes, continues. *Even while the brain is losing cells* (in middle age) *its level of function is still rising*. In many fields, of scholarship and research and the professions, a man may reach the apex of his level of performance only in the forties, fifties or sixties. Intelligence certainly does decline, in some of its functions, from 25 or 30 onward, paralleling the loss of cells in the brain; but not in all functions, and especially not in the area of a man's special competence. Intelligence tests themselves show an effect of this kind: some tests show a fall from the twenties onward, others do not; and we can now see better the psychological meaning of this fact.

Speculations Concerning the Thought Process

So far so good. But all this skirts a fundamental difficulty. A large brain injury need not reduce intelligence in proportion to its size, because of the conceptual development that has occurred before the injury. But *how?* What is a "concept," neurophysiologically? All this did was to replace one nagging problem with another, for psychological theory had no suggestion to make concerning the mechanism of a conceptual activity, nor the mechanism of related functions such as attention, purpose or insight.

The state of psychological theory was in fact quite unsatisfactory. Lashley in 1930 had brought tumbling down the card-house of earlier theories of the neural basis of behaviour, and none but the most tentative and vague formulations, in neural terms, were being made as a replacement. Psychology had burnt its theoretical fingers, and now was more than cautious.

This is despite the fact that the theoretical impasse had originated in the unsatisfactory, or insufficient, physiology of the day. Instead of attacking the physiological problem directly it was avoided. Some psychologists decided that theory should be dropped altogether in favour of a descriptive science (if there is such a thing); others theorized, but in very general terms

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indeed. The formulations, when definite enough to be intelligible, were in deep conflict. On the one hand were theories that could deal with learning but not perception and thought. On the other were theories designed in the first place to deal with perception, but which failed to deal with learning, or with the crucial question of how a percept or a concept determines response. Few writers seemed aware of the fundamental problem that this cleavage constituted; Lashley is outstanding in his emphasis on this point, his interference-pattern hypothesis (Lashley, 1942) being specifically designed to deal with the relation of perception to a learning process (though he never found a solution for the control of response by perception).

In my worrying about these problems, however, I had a very definite advantage, being forced to physiologize by the need of an explanation for the brain-injury data. About this time, also, Lorente de Nó's conceptions of synaptic function and of reverberatory circuits were becoming known. Hilgard and Marquis (1940) had drawn attention to some of the possibilities of the reverberatory circuit, for psychological theory, and it seemed that Lorente de Nó's (1939) idea of the need of summation at the synapse provided a clue to the selective operation of "set" or "attention." On this foundation, then, my attempted solution for the problem of higher mental processes (Hebb, 1949) was built.

The long and short of the theory is that an elementary idea consists of activity in a complex closed loop called a "cell-assembly," developed as the result of repeated stimulation during childhood; that one or more of these, simultaneously active, can excite another, in a series called a "phase sequence"—that is, a train of thought—and that Lorente de Nó's need of summation for synaptic transmission, in the operation of these cell-assemblies, accounts for the selectivity and directedness of the train of thought.

The theory as published has serious shortcomings. Some are specific to this particular formulation; others, to which we shall return, are more general and may be encountered by anyone working in this field—anyone, that is, who is attempting a theoretical explanation of the more complex brain processes.

First, the obvious defects, the gaps of knowledge in my theorizing of 1949—or of 1944 and 1945, when it was first worked out. I could not assume the primary inhibitory process since demonstrated directly by Brock, Coombs and Eccles (1952), though it would have helped; Peter Milner (1957) has since produced a more adequate conception of the cell-assembly, incorporating in it the inhibitory action of Golgi Type-II cells. Also, my discussion of the EEG assumed that slow waves are the envelopes of spikes, which Li and Jasper have shown is quite wrong. But the greatest omission of all is of course the brain-stem arousal system of Moruzzi and Magoun (1949) whose fundamental role in all higher pro-

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cesses is now clear. No account of intellectual processes and their relation to the brain can be taken seriously today when this is omitted from the reckoning.

We can see now, with hindsight, that there were a number of premonitory signs of this development. Among psychologists, Duffy had argued as early as 1934 that arousal, or level of excitation, should be separated from the question of the direction taken by behaviour. A notion of this kind goes back at least to Head and Holmes ("vigilance"), whose views were re-emphasized in 1936 by Krechevsky (though the vigilance function was ascribed to the cortex, not to the brain-stem).

From a physiological point of view, the work of Ranson and Bremer and their collaborators led in the same direction. Morison and Dempsey (1943) were getting very warm indeed; and it seems clear that Jasper and Fortuyn (1947) and Hunter and Jasper (1949) were on the verge of the discovery made by Moruzzi and Magoun, but for the accidents of serendipity. Hunter and Jasper's arrest phenomenon itself stands as a major discovery whose full importance for the theory of behaviour seems not yet to be recognized. There is one other name I have not mentioned—namely, Penfield—but I will return to his work later, when I come to the question of the hazards and difficulties of the theorizer in this field, and of the function of theory in behavioural research. As we shall see there are difficulties with his formulation (Penfield, 1938), but to the best of my knowledge he was the first to conclude that the brain-stem is of primary psychological significance, intrinsically concerned in higher mental processes and not merely an avenue of access to the cerebral cortex.

The generalized significance of the nonspecific projection system for psychological phenomena was formulated by Lindsley (1951), in his "activation theory of emotion." We are still a long way from understanding the problems of emotion and motivation, but Lindsley's proposal was a definite break-through for theory. In effect, emotion is equated with activity in the arousal system. Such a statement may be overly simple as it stands, but it has two great virtues. It is definite and intelligible, and instead of blocking further thought it is such as to invite elaboration; the very gaps in the theory are such as to stimulate new research to close them, as in the work of Sharpless and Jasper (1956) or Olds and Milner (1954).

Our concern today is with the nature of thought and intelligence, so this is not the place for a discussion of emotion as such. But another virtue of the activation theory is that it makes a close connexion between emotional and intellectual processes. If we identify emotion with the level of activity in the arousal system, what we are saying is that some degree of emotional tone is an integral part of thinking, because we know that the cortical processes of thought cannot exist by themselves; the arousal system must be active. We are also saying that a moderate degree of emotional activation is organizing and integrating in its effect on thought

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—a point that has long been insisted on by a number of writers—but we can also understand, at least hypothetically, how an excessively *high* level of activation may be disorganizing, even paralysing (Hebb, 1955).

It is in this context that Hunter and Jasper's demonstration of behavioural arrest seems of particular importance psychologically. There is a class of phenomena that we are only beginning to understand—or to be able to think about, at least—but of the highest practical significance at certain times in human affairs. There are certain situations, usually involving threat of some kind, in which the thought process is crippled or paralysed. There may also be bodily paralysis, the person simply being unable to move; what I refer to as a "paralysis of thought" is what happens when the person under threat is quite able to stand up and move his limbs but engages in aimless activity, or does nothing, instead of making the movements that would ensure his escape or lessen his danger (Marshall, 1947; Tyhurst, 1951). It is the *power of decision*, or the "will," that is impaired.

Study of behaviour in battle shows, for example, that there are only about 15 per cent—the figure varies between 10 and 25 per cent—of riflemen who can be counted on to fire their rifles in the general direction of the enemy when in actual combat. This is not a question of "cowardice," because the man who does not fire does not run away, and is apt to run greater risks than those whose behaviour is more efficient. The problem of the company commander is to identify the men whose mental processes remain organized in combat, so they can be distributed throughout the company and provide a stimulus, an organizing influence, for others. There is a similar problem in the training of the fighter pilot who is entirely adequate up to the moment when, in combat, the enemy plane is within his sights—and who then fails to press the firing button. There are of course complications in all this; it appears for example that one inhibitory factor is the knowledge that to fire in combat is to take human life, unlike firing during training. But it also appears that there is what we can call a "crisis effect," not unlike stage fright, which can produce a failure of the thought processes that lead to effective overt behaviour.

The military problem does not exist only at the level of the actual combatant, the front-line soldier or fighter pilot; there is a good deal of evidence to indicate that the commanding officer is vulnerable to the same kind of dissolution of his powers of planning and decision in the face of the enemy. Evidently, the disruptive factor here is not physical danger. It is not a fear of physical pain, or of death, that makes the difference between the fighting commander and the one whose resolution and clarity of thought are impaired in battle. It seems rather to be the disrupting effect of the "big decision": the same lack of resolution when the chips are down that distinguishes the first-rate assistant in politics from a Prime Minister, the weakness that marks the man who is excellent as vice-president of a corporation and breaks in the presidency.

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Actually, of course, we have little direct knowledge of what happens in these more dramatic examples of the effect of emotional pressure on intellectual processes. Behaviour in civilian disasters or in battle, and the difficulties of the executive, serve to show some of the dimensions of the problem; but our hope of learning more is likely to lie in less dramatic laboratory studies.

If I am right in thinking that these are examples of what I have referred to as a crisis effect, we may be able to get at the effect in other forms: for example stage fright (Paivio and Lambert, 1959). And if I am also right in my deep conviction that the direct study of brain function contributes essentially to psychology (but is not a substitute for it), then we can hope also that new leads for human experiment, and the understanding of such problems, will come from the work going on here and elsewhere concerning the relation of activity in the arousal system to cognitive processes and overt behaviour. In addition to studies already mentioned, particularly those of Hunter and Jasper, Sharpless and Jasper, and Olds and Milner, I should mention other recent work by Fuster (1958) showing that perception can be improved by brain-stem stimulation; and by Glickman (1958) and Mahut (1957), who have produced defects of memory and of insightful learning, by various conditions of subcortical stimulation in the conscious, normally active animal. These studies are all far from practical applications; at present they are also far from making a coherent picture theoretically; but they supply new pieces in the puzzle-picture we are trying to put together, and in the long run there is nothing more practical than the pure research which sets out simply to understand, rather than providing immediately useful answers.

The Role of Theory in Neuropsychological Research

And now finally I turn to the question of theory, as an indispensable tool by which pure research achieves its results. The additions to knowledge which have been made in the past thirty years allow us to deal in more realistic and comprehensive terms with thought and behaviour, but they have also complicated our problems enormously. The complexities face anyone who proposes to do research in the field, and it is only by the wise use of theory that one can hope to deal with them.

Behavioural research—neurological, physiological and psychological—is reaching a new level of maturity. Its significance for human concerns outside the clinic or laboratory is spreading, and shows up sometimes in the most unlikely places. The isolation experiments of Bexton, Heron and Scott (1954) and Heron, Scott and Doane (1956) originated on the one hand from the theory of brain function, and on the other relate to such diverse topics as brain-washing, the monotony of long-distance truck-driving (Mosely, 1953), and the future behaviour of human beings cooped up in space vessels. It is no longer idle fantasy to raise, as a problem for

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consideration, the possible relation between the activity of the brain-stem reticular formation and the behaviour of the front-line soldier who does not raise his rifle to hold off the enemy, or the man who is killed in traffic because paralysed by impending disaster. We need no longer strain for such connexions, such points of correspondence between theory and behaviour outside the laboratory. The very maturity of theory, however, demands sophistication in its use, an understanding of its limits as well as its powers; and this is hard to achieve wherever "mind" is concerned.

In the twilight zone between neurology and philosophy, for example, there is a group of writers who seem emotionally committed to a defence of the soul as against any mechanistic theory of man. I say emotionally, because the discussion is not conducted as one would expect if a theory from geology or biochemistry were in question[1]. Common opinion or ancient theory is cited as evidence, technically relevant evidence favouring the other side of the argument is not dealt with, and the aim seems to be to make the opponent's position look ridiculous rather than to clarify the issues involved. Part of the explanation, apparently, is that theory has been confused with belief, and wrong beliefs must be attacked by any means at hand.

Logically, however, theory is not an affirmation but a method of analysis, and cannot prejudice any belief. Knowledge progresses by stages, so the theory one holds today must be provisional, as much a formulation of one's ignorance as anything else, to be used as long as it is useful and then discarded. Its function is to organize the available evidence and guide the search for better evidence. It is really only a working assumption, which the user in fact may actively disbelieve[2]. There is no neuropsychological theory at present that does not have grave defects, and thus no danger that such theory will "disprove" the theory of an immaterial mind or soul, for a long time to come at least. One's beliefs therefore need not prejudice one's choice of working method. One is free to work with any theory

[1]Consider for example the logic of a statement by Cohen (1957, p. 18): "Actually, the irreducibility of mind to brain is beautifully exemplified in the experience of pain, for without *awareness* there can be no pain." The statement is a *non sequitur:* we can agree that pain does not exist without awareness or consciousness, but this does not tell us what awareness consists of, whether it is an attribute of the soul or a part of the brain's activity. It seems that Professor Cohen has begged the question completely, for the statement is quite irrelevant unless one has unwittingly assumed that awareness cannot be a brain function—the point he is trying to prove.

[2]I may hold to the existence of an immortal soul as an agent in man's behaviour which, be it noted, is an intellectually respectable position for either scientist or non-scientist. If so, my best hope of demonstrating it is to assume that no such agent exists, with the expectation that ultimately the assumption will be found insufficient (that, in the final analysis, some features of man's thought and behaviour will not be explicable in these terms). This is the null-hypothesis procedure of statistics, or Euclid's *reductio ad absurdum.* Objecting to use of the null hypothesis because one does not believe it is an absurdity.

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that is conducive to research and likely to clarify fundamental issues—even if it does so by producing evidence that in the end shows the theory itself to be wrong.

Now the mechanistic theories have been the productive ones in this century, and they have not yet shown themselves to be wrong (Lashley, 1958). This brings me to my second main point: the function of criticism is to clarify, not to obscure, and to sort out good evidence from bad. No scientific criticism of mechanistic theory is competent which accepts nineteenth-century philosophic analyses as evidence (especially since those opinions in turn derived from a still earlier neurology) while disregarding twentieth-century analyses (such as those of Feigl, 1951, Lewis, 1929, and Ryle, 1950); and still more, disregarding the implications of psychological studies, such as those of the Würzburg group, as exemplified in the discussion by Humphrey (1951) or Boring (1953). Sober and careful analysis of controlled introspective data indicates that man is not directly conscious of his consciousness, that the nature of his conscious processes must be examined inferentially instead of by direct observation. One perceives objects and events; one does not perceive the sensations or perceptions arising therefrom. To ridicule mechanistic theory on the ground that everyone knows what his own consciousness is like, therefore, with no mention of the opposing evidence from technical studies, is not performing the function of scientific criticism: in place of evidence it puts theory, and outmoded theory at that.

Thus we still find writers (e.g. Eccles, 1953; Smythies, 1957) regarding as established fact what may be called the *theory of the imprisoned knower*, the thinker encapsulated in his own field of consciousness, who has knowledge of an outside world only by means of difficult—and indeed uncertain—inference. On the face of it this is a theory of perception only; but it has been taken to imply a theory of knowledge which can be, and sometimes is, regarded as a decisive objection to mechanistic hypotheses of consciousness. With certain tacit assumptions that were made historically the theory may be an inevitable conclusion: but only after making those assumptions, so this is still theory, not factual evidence. It may perhaps be tenable, if some flaw can be found in technical analyses such as Humphrey's, but it is in sufficient doubt not to be itself a refutation of other theory.

Still less a contribution to clarity is Walshe's (1957) critique of Penfield's theorizing. The theory undoubtedly has its defects, but so has the criticism: first as criticism, and secondly in misrepresenting some fundamental issues. Instead of giving us a better picture of the strengths and weaknesses of Penfield's work, this paper obscures the picture, by combining some sound criticism with a series of debater's points. One may agree with Walshe that it is unsatisfactory to localize consciousness in the brain-stem (Penfield, 1938); but if Penfield's early proposition went too

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far, it seems that there was still an important element of truth in it, in the light of all the results of the past ten years following the discovery of Moruzzi and Magoun. There are also difficulties about the treatment of memory, and the separate localization of "recording" and "recall" (Penfield, 1954). But somehow the theoretical climate in which Penfield works has led him to the observation of some remarkable phenomena that others, with similar opportunities, did not observe (or perhaps did not perceive as having theoretical significance). Walshe might have given us a balanced appraisal of this body of work, which would have been of great value. Instead we have the trivial comparison with Carpenter, who also placed consciousness in the brain-stem a century ago: this is no more cogent, as criticism, than it would be to attack Walshe's dualism on the ground that Augustine or Aquinas was a dualist even earlier.

More important than the mode of criticism, however, are the implications that this paper (Walshe, 1957) has for the scientific method in psychology. It is clearly implied that scientific investigation proceeds first by the collection of facts, and arrives secondly at generalizations from the facts. Speculation and the *a priori* postulate are both ruled out. This is the classical view, deriving from Bacon, but it has been known for some time to be false. No research that breaks new ground will be done in this way; the collection of facts, from which to generalize, demands the guidance of imaginative speculation. Walshe, for example, uses the phrase "speculative hypothesis" as disparagement (p. 538: what other kind of hypothesis is there?), and deplores the current situation in neurophysiology in which "speculation still runs ahead of fact" (p. 517). The true question is, What kind of speculation? and on this point we are given no real help.

Finally, on the mind-body problem, Walshe deplores physiological conceptions of conscious states, and recommends instead Hughlings Jackson's parallelistic philosophy. He objects to equating psychological and physiological categories, neglecting the fact that Jackson did so constantly, and the further fact that this is exactly what parallelism permits—or rather, requires.

In an empirical scientific context, parallelism is no more than a convenient verbal device for avoiding epistemological argument. It is *not* a philosophy that removes the problem of consciousness from the ken of neurological analysis. Interactionism does so, for it says the final control of man's actions is not in the brain but in the soul, so behaviour does not have to be explained by neural action. But parallelism says that the soul does not act on the brain: the activities of the two flow along side by side in time, but everything man *does* is accounted for by the physiological processes of brain and body. To understand behaviour, therefore, we must have an account of the higher neural activity "correlated with" consciousness. Every shade of meaning or nuance of expression, every

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generous thought or poetic insight conveyed to others in speech or writing, is wholly determined by the physiological mechanisms of the body. Thus the parallelist (like the epiphenomenalist) faces exactly the same problem as the materialistic monist in dealing with the subtleties of behaviour. Jackson did not avoid the problem, and it is absurd to cite him in support of a different attitude—except that by invoking parallelism he cannily avoided the contumely that goes with being known as a materialist.[1]

For us today Hughlings Jackson's significance lies in that effort to bring together psychological and neurological conceptions as well as in his brilliant observations on aphasia and the epileptic march. We are still involved in the same task, which has indeed become more difficult as our knowledge has increased. It is evident from his endless qualifications and disclaimers that Jackson felt uncomfortable about some of his speculations. Nevertheless he made them and published them, and they have been affecting our thinking ever since. Traditionally the theorist has tried to persuade us that his statements represent truth, as a necessary consequence of observed fact, and traditionally the critic has asked whether this is logically so or not: if true, the theory is to be enshrined, and if false thrown out entirely. Today we are more sophisticated and hardly expect theory to provide a segment of final truth about the universe. This may permit the theorist to be less uncomfortable than Hughlings Jackson about his speculation, but it does complicate the problems of the critic.

As to the neurological and mechanistic type of theory, I have tried to say two things: first, it is not a necessary inference from facts, and quite conceivably it will turn out in the long run to be false; but secondly, it is the clarifying line of thought, and for some time it has been the productive line as far as research is concerned. It deeply implicates psychology in neurological matters, and vice versa; and it demands of us that we make greater efforts at communicating with one another. I have emphasized the significance of neurological ideas for psychology, and it must be conceded that psychological thought has sometimes been abortive because of not keeping abreast with neurological developments. But this is a two-way street; the neurologist must likewise keep in touch with the developments of psychological knowledge, for some of the most important evidence concerning the nature of brain function can only be obtained from the study of behaviour.

[1]See for example the passage that Martin (1949) quotes from Jackson, beginning "To lose consciousness is to lose the use of the most special of all nervous processes whatsoever . . ." Or for that matter, the passage from which Walshe himself quotes, somewhat inaccurately, which begins "The question is, how far down in the nervous system there are psychical states during nervous activity. Is the brain the organ of mind, or only the chief part of that organ? I give no opinion on this difficult question." Formally, the position is parallelism, whenever Jackson stops to make a formal commitment; but at other times the language and thought are indistinguishable from a modern assumption of monism, as parallelism in effect requires, in dealing with behaviour.

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CEREBRAL DISSECTING ANEURYSMS

BY

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"A DISSECTING aneurysm is the lesion produced by penetration of the circulating blood into the substance of the wall of a vessel with subsequent extension of the effused blood for a varying distance between its layers. In most cases the aorta is the vessel involved, though dissecting aneurysms can form in the pulmonary artery and in all grades of arteries down to the small perforating arteries of the brain" (Shennan, 1934). This statement indicates that the occurrence of dissecting aneurysms in the brain has been recognized but there are very few well documented examples in the literature. The ætiological factors in these reported cases vary but in several they are obscure. In this paper a further three cases recently encountered are recorded and by histological examination it has been possible to establish the mechanism of the dissection. Previously reported examples are reviewed and from this analysis several salient clinicopathological features emerge which help to clarify the diagnostic problem set when a "stroke" occurs in a young individual. An additional case, probably of similar nature, is also reported as it illustrates the clinical difficulties and a possible therapeutic approach, although the diagnosis could not be confirmed.

CASE REPORTS

Case 1.—A youth, aged 16, worked as an apprentice electrician until four days before his death. In his job he had to climb up and down 200 steps carrying things. After finishing the day's work he complained of severe headache and he vomited. While riding home in a van he appeared to fall asleep but by the time of arrival at his house, it was impossible to rouse him. In the previous week he had complained of frontal headaches and recently he had experienced several nose bleeds. A month before he had developed a dental abscess necessitating the removal of a wisdom tooth. There was no previous history of fits, injury or meningitis. He was left handed.

Physical examination.—He was very drowsy although responding to painful stimuli on the right side by withdrawal. The left side was immobile. There were no abnormal physical signs on general examination and the blood pressure was 120/80 mm. of mercury. The optic discs appeared normal and there was a profound left hemiplegia, involving face, arm and leg. He was severely aphasic.

Investigations.—The EEG showed high amplitude 2-5 c/s activity in the right

parieto-temporal region indicating the presence of a lesion in this area. The ECG was normal apart from sinus bradycardia of 42 per minute. A blood count showed 100 per cent hæmoglobin (16 grammes/100 ml.) and 13,000 white cells per c.mm. (80 per cent polymorphs, 18 per cent lymphocytes and 2 per cent monocytes). The blood urea was 25 mg./100 ml. A lumbar puncture revealed clear C.S.F. containing 2 lymphocytes and 20 red cells per c.mm. It also contained 35 mg. per cent of protein, 760 mg. per cent of chloride, 60 mg. per cent of sugar and gave a negative Pandy test. The W.R. was negative in both C.S.F. and blood. X-rays of chest and skull were normal. A right percutaneous carotid angiogram was performed under a general anæsthetic three days after the onset of his illness. This showed a block of the terminal part of the internal carotid artery so that neither the anterior nor the middle cerebral arteries filled although the anterior choroidal, and posterior communicating and posterior cerebral arteries were outlined. The internal cerebral vein was displaced to the left presumably by œdema associated with infarction. No cause for the carotid occlusion was apparent Death occurred the following day.

Necropsy.—The site of the dental extraction had healed satisfactorily and there was no dental sepsis. The lungs showed marked congestion and œdema. The heart and kidneys appeared healthy and showed no evidence of hypertensive changes. There was congestion of the liver and spleen. The brain (weight 1,560 grammes) appeared extremely swollen with flattening of the convolutions and narrowing of the sulci. This was maximal in the right central region surrounding the Sylvian fissure and was due to infarction in the territory of distribution of the middle cerebral artery. The swelling of the right hemisphere had caused herniation of the right gyrus rectus into the prechiasmatic recess, tentorial herniation of the right hippocampal uncus, and herniation of both cerebellar tonsils. There was arched displacement of the mid-line structures convexly to the left with narrowing of the right lateral ventricle to a slit (fig. 1). No aneurysms were seen and there was no sign of subarachnoid hæmorrhage. Both internal carotid arteries were healthy and widely patent, both in the neck and in the cavernous sinus, while the circle of Willis appeared free from atheroma. The right middle cerebral artery was turgid, swollen and dark blue in colour while the proximal part of the anterior cerebral artery showed similar features extending to the junction with the anterior communicating artery. On sectioning these vessels the lumen appeared completely occluded with thrombus.

Microscopic findings.—The area of recent infarction involved the right insula cortex and white matter, claustrum, external capsule and posterior half of the putamen. Numerous shrunken hyperchromatic nerve cells were present in the affected area and there was a slight polymorph reaction in the softened tissue with a few petechial hæmorrhages in the cortex. The appearance would be compatible with a duration of softening of about four days. A smaller area of softening of similar appearance involved the cortex and superficial white matter on the medial aspect of the right frontal lobe but this had not been noted macroscopically.

The thrombus in the middle cerebral artery was found to be not in the true lumen of the vessel which was still patent although narrowed, but in the false cavity of a dissecting aneurysm (fig. 2). In view of this finding, the whole of the proximal parts of the middle and anterior cerebral arteries were sectioned serially. From a study of these sections it was seen that the dissection occurred between the internal elastic lamina and the muscle coat and extended peripherally from the origin of the middle cerebral artery to its smaller pial branches in the Sylvian fissure. It had originated at the bifurcation of the internal carotid artery at the site of a congenital defect in the wall (fig. 3). There was at this point a minute aneurysm which had not protruded beyond the adventitia but was entirely within the thickness of the wall of the vessel bulging through the defect in the media (fig. 4). It was lined by intima and internal elastic lamina but at one edge the intima was thickened and the internal elastic lamina split

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into several strands and at this point the dissection had commenced separating the layers of the frayed internal elastic lamina (fig. 5). It had spread also into the anterior cerebral artery and its proximal branches as far as the anterior communicating artery where it reconnected with the true lumen through a break in the internal elastic lamina. In the segments of the arteries showing dissection the true lumen was still patent although narrowed to a minute slit but fibrin thrombus had been deposited in the false channel. All the other larger cerebral vessels were sectioned and appeared healthy.

Comment.—This case demonstrates the occurrence of a stroke in a young healthy male resulting in a profound hemiplegia and loss of consciousness. In the absence of trauma, hypertension, cardiac or generalized disease the cause was difficult to ascertain although in view of the previous dental extraction a septic embolus was considered. Angiography confirmed the presence of a complete block in the terminal part of the internal carotid artery but gave no indication as to its cause. Even autopsy which demonstrated the infarction and the occluded vessels did not provide an answer and it was not till the microscopic sections were examined that the true cause was found to be a dissecting aneurysm which had originated in a congenital defect of the wall at the terminal part of the internal carotid artery. At the site of the defect in the media there was a minute aneurysm covered by adventitia but still remaining intramural and this had ruptured intramurally. The dissection occurred between the layers of the internal elastic lamina which was split into several thin strands just adjacent to the neck of the aneurysmal sac, but beyond this it spread in the plane between media and internal elastic lamina. It is problematical whether the exertion involved in this youth's occupation played any part in initiating the dissection.

Case 2.—A girl aged 19 was referred to the Neurosurgical Department from the local Mental Hospital because of behaviour disorder associated with epilepsy and an infantile hemiplegia. She was an only child born at full term after a normal pregnancy when her mother was 25 years old. The baby was born as a vertex presentation four days after the mother had been admitted to hospital in labour following a small hæmorrhage. An episiotomy was necessary but forceps were not used. The infant weighed 7 lb. at birth and appeared normal. It was noted some time later that she held her right hand clenched although she moved the arm. By the age of 3 months the child was thought to be a spastic and exercises were prescribed for the right side. She grasped everything with the left hand and was obviously left handed. At the age of 9 months she had her first fit. Another fit occurred at 3 years of age and she was put on phenobarbitone which had been continued to date. The child learned bladder control at one year and was able to walk at 18 months. She did not talk till she was 5 years old. She started at an ordinary school but owing to her spasticity and slowness in mental development she was transferred to a special school for the physically handicapped where she learned to read and write and was of average ability. She was described by her mother as being a highly-strung affectionate child but when her menstrual periods started at the age of $11\frac{1}{2}$ she became bad tempered, aggressive and difficult to manage. Her fits became more frequent after puberty changing in type to a *petit mal* attack each month. She left school at 16 and obtained a job as a knife packer. She was a good worker but her behaviour at home became more violent, destructive,

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abusive, restless, emotional and aggressive, necessitating admission to a mental hospital.

Physical examination.—She did not appear to be of subnormal intelligence although retarded scholastically. There was a right infantile spastic hemiplegia with much smaller limbs on this side. The right wrist was kept flexed with the thumb adducted into the palm and there was limited movement at the elbow and shoulder. The leg was much less involved than the arm. The reflexes were increased on the right with an extensor plantar response. The rest of the examination was normal. The blood pressure was 120/75.

Investigations.—The EEG showed widespread dysrhythmia with scattered spikes and frequent burst of 3–5 c/s waves in the left temporal region. There was some normal voltage activity on the right side and suppression on the left. Over-breathing resulted in a more marked build-up on the right than on the left side. X-ray of skull was normal and a cisternal encephalogram showed dilatation of the left lateral ventricle with a localized lateral protrusion in the central region. The C.S.F. was normal and W.R. was negative. The blood and urine examinations were normal

Operation.—A left hemispherectomy was carried out.

Progress.—Post-operatively she became deeply comatose with bilateral extensor plantar responses. Extradural and subdural blood clot was evacuated through burr holes four days later. She also developed a venous thrombosis in the left leg which impeded her rehabilitation. She was able to move all four limbs and to get about with the aid of calipers. Although she seemed to lack drive and initiative and was often dirty in her habits, her mother thought that she was much more placid, calmer and less emotional. She has improved steadily since and is now walking unaided, with a hemiplegic gait.

Macroscopic examination of left hemisphere.—The specimen received measured $14 \times 9 \times 4{\cdot}5$ cm., and weighed 228 gramme. There was marked atrophy of the cortex of the convolutions surrounding the Sylvian fissure in the central region in the territory of distribution of the middle cerebral artery. The affected area had lost its convolutional pattern and had sunken below the surrounding gyri (fig. 6). The overlying pia arachnoid was thickened, opaque and wrinkled. The surrounding convolutions appeared intact. The lateral ventricle was widely dilated with an additional lateral expansion corresponding to the atrophic area. The middle cerebral artery had been divided between its commencement and its first bifurcation. Its lumen appeared patent.

Microscopic findings.—The atrophic area consisted of dense gliosis extending from the surface of the cortex to the wall of the dilated ventricle, the ependymal lining of which was missing in this lateral part. All nerve cells had completely disappeared and most of the white matter was replaced by dense glial fibres. Only a thin layer of myelinated fibres was present in a few places towards the periphery of the atrophic area in its deeper part. The overlying pia-arachnoid was thickened and contained scattered red cells, lymphocytes and occasional histiocytes containing hæmosiderin pigment. Many dense glial nodules projected into the pia arachnoid over this atrophic zone (fig. 7).

The surrounding cortex of the frontal and occipital lobes and on the superior and medial aspects of the hemisphere had a more normal appearance although there was marked increase in gliosis of the molecular layer and of the subependymal tissue. The white matter although reduced in thickness was well myelinated. In the temporal lobe there was severe cell loss in the Sommer sector of Ammon's horn, consistent with the long-standing epilepsy. The hemispherectomy included the head of the caudate nucleus, lenticular nucleus and the lateral part of the thalamus. The internal capsule showed severe demyelination and replacement gliosis. In the basal ganglia there was

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an increased cellularity due to numerous astrocytes while many of the nerve cells were shrunken and hyperchromatic.

No thrombosed vessels were seen in the pia arachnoid. The proximal part of the middle cerebral artery was serially sectioned. It showed a healed dissecting aneurysm which appeared to have originated at the site of the first bifurcation of the artery in the Sylvian fissure where there was a large segmental defect in the media filled with connective tissue continuous with the adventitia (fig. 8). The internal elastic lamina only partly extended into the defective segment being absent also in a large part. The original lumen of the vessel had been completely obliterated by fibrous tissue in which were several patent capillary channels. The fibrous tissue was surrounded by the internal elastic lamina but on its inner surface this was extremely thin and had disappeared in several places. Although the vessel was widely patent the channel was the false one formed by the dissection (fig. 9). A thin layer of muscle separated the two channels becoming of normal thickness round the new lumen with an incomplete internal elastic lamina on its inner surface. The double muscle coat and elastic lamina indicated the old healed dissection. More distally there was eccentric thickening of the intima with splitting of the internal elastic lamina.

Comment.—Hemispherectomy was performed in a case of infantile hemiplegia with epilepsy for a severe behaviour disorder. Focal atrophy producing a centrally placed porencephalic defect in the territory of distribution of the middle cerebral artery due to old infarction was found. Although most of these encephaloclastic lesions are believed to be the result of occlusion of major cerebral vessels (Courville, 1954) the middle cerebral artery was patent. In its proximal part, however, this lumen was false and the true lumen was displaced to one side and filled with fibrous tissue. Only the double muscle coat and double elastic lamina enabled the true nature of the condition to be recognized. Although no site of rupture could be found so long after the onset there was a gross congenital defect of the media and internal elastic lamina at the first bifurcation of the middle cerebral artery. This is accepted as the cause in the absence of infection, hypertension or generalized disease although trauma to the head during the prolonged labour may have acted as a precipitating factor. Merwarth (1929) believes that distortion of the fœtal head in delivery results in torsion and compression of the major cerebral arteries. In the presence of a congenital weakness such factors could initiate dissection, although no other example has been found in the literature. The only case of a dissecting aneurysm of the middle cerebral artery causing acute infantile hemiplegia was reported by Norman and Urich (1957) but the onset was at 6 months of age.

Case 3.—A married woman, aged 33, was brought into a suburban railway station after a sudden collapse. She was transferred to hospital where she was found to be unconscious on admission.

Physical examination.—Although unconscious, she responded to painful stimuli. Small bruises were seen on the right buttock and over the right iliac crest. There were no signs of head injury and no marks on the throat. Her respirations were regular and easy, and no smell of acetone or alcohol could be detected in the breath. The pulse was regular at 96 per minute and the blood pressure was 110/60. The heart, lungs and

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abdomen showed no abnormality. There was no neck stiffness and the optic discs appeared normal. The pupils were small, central and equal in size reacting sluggishly to light. There was no facial asymmetry. The tone on the right side was slightly greater than on the left and this was more marked in the upper limbs. All the reflexes were brisk slightly more on the right than on the left. The abdominal reflexes were absent and there was an extensor plantar response on both sides.

Investigations.—The urine contained a trace of acetone but no sugar. A lumbar puncture revealed a clear fluid under pressure of 150 mms of water It contained 30 red blood corpuscles per c.ml., but no white cells, 98 mg./100 ml. of protein, 67 mg. per cent of sugar and 730 mg. per cent of chlorides. The blood sugar was 111 mgm. per 100 ml., and the blood urea 18 mg. per 100 ml. A blood count showed 100 per cent hæmoglobin (14·8 gramme) and 11,000 white cells per c.ml. The E.S.R. was 16 mm. in one hour. A further urine examination showed no sugar or acetone, but revealed the presence of 25 mg. of albumin per 100 ml. It also gave a positive qualitative test for barbiturate. X-ray of chest and skull appeared normal. The W.R. was negative in both blood and C.S.F.

Progress.—She remained comatose and developed conjugate deviation of the eyes to the left. The reflexes became equally accentuated with bilateral ankle clonus. On painful stimulation, the arms extended with the forearms strongly pronated. She developed difficulty in swallowing and her respirations became stertorous. She died seven days later. The only additional information obtained from the husband was that previously she had been healthy apart from experiencing some very severe headaches recently.

Necropsy.—Examination revealed no significant abnormality apart from the findings in the brain which appeared to be consistent with a basilar artery thrombosis.

The sectioned brain (1,390 gramme) was received for further examination. The upper pons and mid-brain showed a large area of softening in the mid-line in the tegmentum extending more to the right side in the ventral part. There was hæmorrhagic infarction of the folia of the upper surface of the right cerebellar hemisphere. The cortex of the medial aspects of both occipital lobes was soft on palpation and showed hæmorrhagic infarction. The cerebral hemispheres appeared swollen with flattened convolutions and narrowed sulci. The basilar artery was distended by recent thrombus which completely occluded the lumen. Its wall appeared healthy and devoid of atheromatous plaques. The vertebral arteries were patent and healthy, but the thrombus extended into the proximal part of both posterior cerebral arteries. The circle of Willis was free from atheroma and the major cerebral arteries were healthy and patent.

Microscopic findings.—The extensive softening in the brain-stem was confirmed. Scattered histiocytes were present in the sharply demarcated areas of infarction and together with lymphocytes cuffed some of the vessels. The appearance of the infarction was compatible with a duration of about one week. No thrombosed vessels were seen in the brainstem. A section of the cerebellum confirmed the softening of several folia in the right upper surface involving both cortex and superficial white matter. The Purkinje cells had disappeared in the affected folia, while the granular cells were markedly reduced. Several petechial hæmorrhages had occurred into the softening which appeared to be of a similar age to that in the brain-stem. No thrombosed vessels were seen but over the softened folia a small pial artery, a branch of the superior cerebellar artery, showed a dissecting aneurysm with blood between the internal elastic lamina and the media. The original lumen was still patent. There was similar hæmorrhagic softening of the cortex and superficial white matter on the medial aspect of both occipital lobes extending round the occipital pole to the lateral surface and sharply demarcated from the adjacent intact tissue. The posterior cerebral arteries and

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many of their branches in the pia arachnoid showed a dissecting aneurysm (fig. 10). The true lumen was reduced to a slit-like cavity which was still patent while the dissection had occurred between the internal elastic lamina and media. Although in most of the involved vessels the false channel was widely patent and filled with blood, in the proximal part of both posterior cerebral arteries the false channel was filled with recent fibrin clot in which were many red cells (fig. 11). Areas of softening were found also in both thalami.

Serial sections of the basilar artery showed that the thrombus seen macroscopically was not actually in the lumen of the vessel but was outside the lumen between the internal elastic lamina and the media (fig. 12). The true lumen was compressed to a narrow slit-like cavity displaced to one side and surrounded by the internal elastic lamina. The false lumen was filled with fibrin thrombus in the meshwork of which were numerous red cells and occasional white blood corpuscles indicating its recent origin. The dissection involved the whole of the basilar artery but not the vertebrals. It appeared to have originated at the rostral end where there was a congenital defect in the media at the bifurcation. The dissection had spread into both posterior cerebral arteries and the right superior cerebellar artery. Thrombosis in the false channel had occurred in the proximal part of both posterior cerebral arteries as far as their first bifurcation beyond the junction with the posterior communicating arteries.

Comment.—The relatively sudden onset of coma in a young healthy woman raised several possible diagnoses in the initial stages but the bilateral pyramidal signs and contracted pupils indicated a brain-stem softening due to basilar thrombosis and this appeared to be confirmed by the autopsy. The absence of any generalized or local cause for the thrombosis in a young individual led to further histological investigations and this revealed that the basilar occlusion was in fact due to a dissecting aneurysm originating in a congenital defect in the wall at the upper end. The dissection had spread into the posterior cerebral arteries and their branches and into the right superior cerebellar artery but not into the smaller penetrating vessels. The appearance of the dissection in any one of these smaller pial arteries, with blood between the muscle and elastic lamina could easily be misconstrued as an artifact due to processing or sectioning, but the involvement of many adjacent branches and serial sectioning of a vessel even though it appeared to be obviously thrombosed, indicated the true condition.

Case 4.—A previously healthy married woman, aged 25, suddenly collapsed falling to the ground where she was found complaining of intense headache. She was put to bed but on the following morning she could be roused only with difficulty. She could neither speak nor move the left arm and leg. She was right handed.

Physical examination.—She was conscious but drowsy with the head turned to the right. The optic discs appeared normal. There was aphasia with a profound left hemiplegia, neck rigidity and a positive bilateral Kernig's sign. Pulsation in both carotid arteries was felt in the neck. General examination revealed no abnormalities and the B.P. was 125/85.

Investigations.—The EEG showed periods of generalized suppression of activity alternating with bursts of generalized slow waves without definite focal abnormality. The ECG showed right axis deviation but no evidence of heart disease. The blood count was normal and the W.R. negative. The blood urea was 31 mg./100 ml. Right

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percutaneous angiography showed a complete block of the middle cerebral artery at the site of its first bifurcation. This was interpreted as due to an embolus in the right middle cerebral artery.

Operation.—Four days after the onset of symptoms, the right middle cerebral artery was exposed under hypothermia. It was swollen and blue at the first bifurcation. The arterial wall was incised at this site and a clot was removed. The artery went into intense spasm but when this had passed the incision was sutured. The stellate and gasserian ganglia were subsequently injected with novocain.

Progress.—Anticoagulant therapy was given. By the evening after the operation she was moving the paralysed limbs but the weakness returned on the second post-operative day. Since then a steady improvement was maintained. Her speech became normal, her walking improved and there was no difficulty in movement of the left hand, apart from some stiffness of the middle fingers. When seen two years afterwards the reflexes were brisker on the left side but there was little disability. The angiogram was repeated on the right side a month after operation. The middle cerebral artery was still blocked but there was reflux filling of the terminal part.

Examination of the thrombus (0·09 gramme).—Serial sections of the clot showed that it consisted of a dense mass of fibrin enclosing red and white blood corpuscles, some of which were degenerate. In the centre of the clot was a short strip of thickened endothelium and a few thin strands of degenerate elastic tissue.

Comment.—The sudden onset of a stroke with hemiplegia in a young healthy woman was found to be due to occlusion of the middle cerebral artery. At the time an embolus was thought to be the most likely cause even though there was a complete absence of any obvious primary source and no previous history of rheumatic fever. Embolectomy was carried out although subsequent angiography showed that the vessel was still blocked with reflux filling of the terminal part. There has been marked clinical improvement in the subsequent two years. In retrospect, in view of the experience gained from the preceding cases, a dissecting aneurysm seems a much more reasonable explanation of the occlusion than embolism. The clot contained a tiny fragment of intima which may have been part of the dissection but the material was too minute for any definite conclusions to be reached. Thus although the diagnosis of dissecting aneurysm is likely by comparison with the other cases, it has not been proved.

Discussion

The first 3 cases demonstrate cerebral infarction due to occlusion of one or more of the major arteries at the base of the brain by a dissecting aneurysm originating at the site of a congenital defect of the wall. Although dissecting aneurysms occur most commonly in the aorta or its branches, they may also develop occasionally in smaller arteries. Their occurrence in the cerebral vessels was described by Ellis (1909) who studied the problem of the miliary aneurysms (Charcot and Bouchard, 1868) in the causation of spontaneous cerebral hæmorrhage. He found that the arterial lesion responsible for hæmorrhage was primarily in the intima beginning in the elastic layer as arteriosclerosis with progressive involvement of the media and adventitia leading to weakening and rupture. A

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circumscribed portion of the wall might give way to produce a dissecting aneurysm. Based on these observations Kaufmann (1929) alleged that dissecting aneurysms frequently occur on the small cerebral vessels.

On reviewing the literature, however, very few cases of cerebral dissecting aneurysm were found. This may be due, in part, to the difficulty in tracing them as the title of many of the articles gives very little indication of the inclusion of a case with an intracranial dissecting lesion. It is also very likely that owing to the common presentation of these cases as cerebral thrombosis with subsequent softening, the careful sectioning of the obviously occluded vessel would not be undertaken or if carried out the finding of dissection would appear to be of small consequence and merely mentioned in the description, if recorded at all. 14 cases of intracranial dissecting aneurysms have been found and for ease of comparison these have been tabulated together with the present 3 proven cases (Table I).

TABLE I.—SUMMARY OF CASES OF DISSECTING ANEURYSMS OF CEREBRAL ARTERIES
(14 reported previously, 3 in this paper)

Author	*Sex and age*		*Arteries affected*	*Aetiological factors*	*Remarks*
Turnbull (1915)	—	—	Right middle cerebral	Acute syphilitic arteritis	Hæmorrhage
Scholefield (1924)	M	47	Right vertebral and basilar	—	Died 15 days after onset of cold
Hyland, Case 2 (1933)	M	42	Basilar	"Mucoid degeneration" of media	Brain-stem softening Died
Hassin (1937)	M	35	Basilar and its branches	Accidental electrocution	—
Szabo (1939)	F	35	Right vertebral	Syphilitic mesarteritis	Brainstem-softening. Died
de Veer and Browder (1942)	M	42	Right middle cerebral	20 ft. fall to ground	Lived 57 hours
Dratz and Woodhall (1947)	F	21	Left internal carotid with adjacent anterior and middle cerebral	Hit by motor-car	Lived 3 days
Ramsey and Mosquera (1948)	M	47	Right middle cerebral	Cystic medio-necrosis and Arterio-sclerosis	Rupture of vessel Massive sub-arachnoid hæmorrhage
Poppen (1951)	—	—	Angular branch of middle cerebral	—	Seen on angiogram, surgically excised confirmed histologically

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Poppen (1951)	—	—	Middle cerebral	—	Seen on angiogram; ligated internal carotid. Well after 8 years. Not confirmed
Sinclair (1953)	F	27	Right middle cerebral	—	Migraine for several years. Died after 4 days
Bigelow (1955*b*)	F	46	Right middle cerebral	Excision of berry aneurysm	Lived 1 day post-operatively
Watson (1956)	M	32	Basilar	Medial degeneration	Brain-stem softening. Died after 4 days
Norman and Urich (1957)	M	15	Right middle cerebral	No indication	Infantile hemiplegia. 6 months
Wolman (1959) Case 1	M	16	Right middle cerebral and proximal anterior cerebral	Congenital defect. Intramural aneurysm	Infarction of insula and frontal lobe. Died after 4 days
Case 2	F	19	Left middle cerebral	Congenital defect	Infantile hemiplegia since birth. Hemispherectomy
Case 3	F	33	Basilar and proximal posterior cerebral	Congenital defect	Infarction of brain-stem, thalami and occipital lobes. Died after 7 days

From this table it will be seen that both sexes have been involved, their ages ranging from birth to 47, with increasing frequency in the fourth and fifth decades. The middle cerebral artery, especially on the right, was most commonly involved (10 cases). The other common site was the basilar artery (5 cases). In the remaining 2 cases the vertebral artery was involved in one while in the other the intracranial portion of the left internal carotid artery was the site with extension in both anterior and middle cerebral arteries. The case described by Northcroft and Morgan (1944) has been omitted as the site of dissection was confined to the first $1\frac{1}{2}$ in. of the left internal carotid artery in the neck, although thrombus spread into the left middle and anterior cerebral arteries and into the left posterior communicating branch.

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Concerning the pathogenesis of cerebral dissecting aneurysms various ætiological factors have been incriminated as in aortic dissections. Because of the rarity of cerebral dissecting aneurysms compared with those of the aorta and the difference in the plane of dissection, most authors have considered that the basic processes must differ in the two types. In the aorta, dissection usually splits the media, often in its outer part. In a study of aortic dissecting aneurysms, Gore (1952) and Gore and Seiwert (1952) found idiopathic degenerative changes in the media with increased vasa vasorum, mild inflammatory reaction and myxomatous tissue. By the rupture of one or more vasa vasorum a hæmatoma was produced in the media resulting in dissection so that an intimal tear was not a necessary initiating factor being absent in 23 out of the 85 cases studied. In the cerebral dissections severe medial degeneration was recorded in only 3 cases and is usually absent. The plane of dissection is subintimal, splitting the internal elastic lamina and separating it from the media. It is therefore to be expected that the ætiological factors are quite different from those operating in the aorta.

Of the possible causes of dissection mechanical injury has been incriminated in 3 cases and syphilitic arteritis was found in 2 of the others. No mention of pathogenesis was made in 3 of the reports while in the case of Norman and Urich (1957) no indication of the cause could be found in spite of serial sectioning of the affected vessel. In the patient described by Sinclair (1953) migraine had been present for several years and it was suggested that focal vascular alteration such as vasoconstriction, dilatation and œdema occurring during the attacks may have acted as the immediate precipitating factor. Only in the case described by Bigelow (1955*b*) was a congenital defect present in the wall associated with a berry aneurysm but the dissection was initiated by the trauma of surgical excision of the aneurysmal sac.

Thus the 3 cases (1, 2 and 3) described in this paper are the first in which a congenital defect in the arterial wall forms the basis of the dissecting aneurysm without there being any definite berry aneurysm or surgical intervention. If the congenital defects in the cerebral arteries which are responsible for berry aneurysms can also lead to dissecting aneurysms, several theoretical implications follow. It is possible for a berry aneurysm to rupture at the site of its attachment forming hæmorrhage in the vessel wall itself instead of rupturing externally to produce subarachnoid or intracerebral hæmorrhage or the two may occur simultaneously (Bigelow, 1955*b*). This may be occasionally a factor responsible for the ischæmic lesions found in the territory supplied by the vessel on which the aneurysm is situated or in more remote areas. Although spasm of arteries is the usually accepted cause (Robertson, 1949) dissection could act either directly by blocking the vessel or by initiating spasm. It is also possible for a congenital weakness to produce an intramural aneurysm as an early

stage in the development of a berry aneurysm. There would be no macroscopic evidence of an aneurysmal sac, yet rupture could occur at this stage to produce a dissecting aneurysm, as in Case 1.

The frequent occurrence of congenital mural defects at the junctions of the cerebral arteries forming the Circle of Willis was first demonstrated by Forbus (1929, 1930) who found areas of complete deficiency in the muscular coat of arteries in about 75% of a group of over 30 normal brains. Such defects were not confined to adults, being found also in children including several babies under 12 months of age and in one stillborn infant. Such defects are now regarded as the primary causal factor in the genesis of aneurysms (Eppinger, 1887; Voncken, 1931; Kahlau, 1937; Schmidt, 1938; Cardona, 1941; Richardson and Hyland, 1941). Although the presence of aneurysms in infants under 1 year is a rare occurrence, the arterial wall defect which is responsible may well be present at the time of birth (Bigelow, 1955*a*). If such defects are also responsible for dissecting aneurysms then those lesions ought to be more common than the review of the literature suggests. Of those recorded there are only 3 in which a congenital defect may have played some part. Bigelow's patient (1955*b*) had a berry aneurysm, but the trauma of excision was the precipitating factor. Brolin and Hassler (1958) have detected minute aneurysms by microdissection and suggest that they occur more frequently than is indicated by the figures in the literature, many being overlooked. It is possible that a minute congenital aneurysm was responsible for both the attacks of migraine and the terminal dissection in the case described by Sinclair (1953) rather than that the migraine caused the dissection. None was found at autopsy nor was such a defect found in the case reported by Norman and Urich (1957) but the extremely young age at which dissection occurred (6 months) suggests a congenital basis, especially in the absence of trauma, infection, arteriosclerosis or hypertension.

The apparent rarity of the condition may well be due to failure of recognition and difficulty in finding the point of dissection. In order to test this assumption the clinical features and mode of presentation encountered in the cases recorded in the literature have been studied together with the present 3 cases. Adequate details are available in 15 instances and in all these the onset was the development of a typical stroke. Death occurred rapidly from massive subarachnoid hæmorrhage in 2 while in the remainder softening in the distribution of the affected vessel was found. Thus cerebral thrombosis is the most likely diagnosis to be made in these cases. When this occurs in a young individual before the age of 50 the differential diagnosis is often problematical (Wolman, 1958) but a dissecting aneurysm must be considered. It is possible that some of the cases diagnosed as cerebral thrombosis or embolism survive and are not examined microscopically, e.g. the true diagnosis cannot be proved as in Case 4. Even in autopsied cases, unless the whole of the vessel supply-

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ing the infarcted territory is carefully examined using serial sectioning, the true cause of the thrombosis may be missed. The same remarks apply to examples of subarachnoid hæmorrhage where no aneurysm is seen and even to cases where the aneurysm is obvious. It is also conceiveable that in many instances the dissection has been interpreted as an artefact, in the same way as defects in the wall of cerebral arteries were thought to be artefacts (Tuthill, 1933). The appearance of the internal elastic lamina lying free in the lumen of the vessel in an isolated section is very suggestive of an artefact produced by sectioning, but when seen in more than one vessel and in several parts of the same vessel, its true significance can be appreciated. It thus seems very likely that many cases have not been recognized and the paucity of examples in the literature does not reflect the true incidence of the condition.

As congenital defects in the wall of the cerebral arteries can be the basis of dissecting aneurysms it is relevant to discuss the anatomical accompaniments which may play an important part. Carmichael (1945, 1950) has suggested that although the developmental factor is important in producing the medial defect, degenerative changes in the intima involve the internal elastic lamina. For the formation of an aneurysm both must occur and it is only by chance that the basic lesions in the intima and media affect the same part of the arterial wall, thus explaining the low incidence of aneurysms compared with the high frequency of developmental defects. A similar explanation may apply to dissecting aneurysms, where the dissection starts in the degenerate intima and extends into the split and reduplicated internal elastic lamina adjacent to this medial defect. Hackel (1928) studied focal intimal hyperplasia in cerebral vessels and found that it was always more marked at points of branching and bifurcation. Defects of the media and aneurysm formation are also commonest at these points. In a study of aneurysmal sacs, Forster and Alpers (1945) found that the elastic layer is very variable, occasionally being present and showing no alteration, but more often being absent, split or fragmented. Adjacent to the neck of the sac or in its margin there is intimal proliferation with splitting of the internal elastic layer in almost all cases (Walker and Allegre, 1954). Thus, although the medial defect is the most striking developmental factor there is usually an accompanying intimal change, and the abrupt ending of this fragmented elastic layer at the neck of the sac would tend to favour dissection if the sac ruptured near its base. The plane of dissection between the internal elastic lamina and the muscle coat would result in occlusion of the lumen rather than massive external hæmorrhage as occurs in the aorta where the media itself is dissected and the lumen much larger. In surviving cases, the new channel formed by dissection develops new layers of elastica in the fibrous connective tissue surrounding it. A thin layer of new smooth muscle fibres may also develop in the wall around the false channel. Similar regenerative changes

have been seen in the healed vascular lesions of acute pneumococcal meningitis (Smith, Norman and Urich, 1957) and are, therefore, non-specific. They do, however, make the interpretation and recognition of the original dissection more difficult.

In acute infantile hemiplegia careful examination of the blood vessels has not often been carried out and in many of the reports no vascular obstruction was found. In several hemispherectomy specimens examined by Bertrand and Bargeton (1957) plaques of subintimal fibrosis associated with splitting of the internal elastic lamina were found in the middle cerebral artery or its branches, while Mair (1952) reported similar findings. The interpretation of these changes varied, some being regarded as due to endarteritis from a previous infection, or to organization of previous thrombus. Other factors such as dystocia and anoxia were also suggested. Congenital arterial defects with the possibility of dissection have not been recognized but their occurrence in infancy should be considered in the differential diagnosis.

SUMMARY

3 cases of dissecting aneurysm of the cerebral arteries are described, in which the dissection commenced at the site of a congenital defect of the wall.

The first, a boy of 16, had a small intramural aneurysm at the terminal bifurcation of the internal carotid and this had ruptured into the wall of the middle and anterior cerebral arteries producing infarction in the territory supplied by these vessels.

In the second case hemispherectomy was performed at the age of 19 for an infantile hemiplegia present from birth. The insula region showed an old infarct due to a healed dissecting aneurysm of the middle cerebral artery at its first bifurcation at the site of a congenital defect of the media.

The third case, a woman of 33, had a dissecting aneurysm of the terminal part of the basilar artery spreading into both posterior cerebral and the right superior cerebellar arteries and resulting in extensive infarction of the brain-stem, cerebellum, thalami and occipital lobes.

14 cases of dissecting aneurysm were found in the literature but in only one of these was the dissection associated with an aneurysm. In the remainder syphilis, trauma or degenerative changes were responsible or no cause could be found.

The rarity of dissecting aneurysms is in striking contrast to the frequency of congenital defects of the wall of cerebral vessels but this may not be a true assessment for several reasons which are discussed.

The clinical features are reviewed and a fourth case is described to illustrate them, although the diagnosis could not be proved owing to the patient's recovery.

It is concluded that as most of the cases present as cerebral thrombosis

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in a young individual, dissecting aneurysm should be considered in the differential diagnosis, especially when heart disease, hypertensive arterial degeneration and generalized systemic disease cannot be found. It is also a possible cause of acute infantile hemiplegia in the absence of trauma, infection, anoxia or generalized disease.

My thanks are due to Mr. J. Hardman, F.R.C.S., under whose care Cases 1, 2 and 4 were admitted, for allowing me full access to his clinical notes on all the cases, and for many helpful suggestions and much advice. Thanks are also due to Dr. R. Weetch, under whose care Case 4 was admitted, for clinical details; and to Dr. G. Forbes, who performed this autopsy, for referring the material. The useful criticism and help with the text given by Mr. A. A. Jefferson, F.R.C.S., is gratefully acknowledged.

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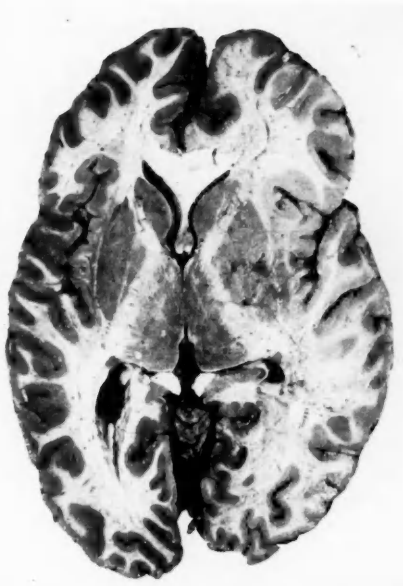

FIG. 1. (*Case 1*).—Horizontal section of brain showing swelling of the right hemisphere due to early infarction of the insula, basal ganglia and frontal lobe.

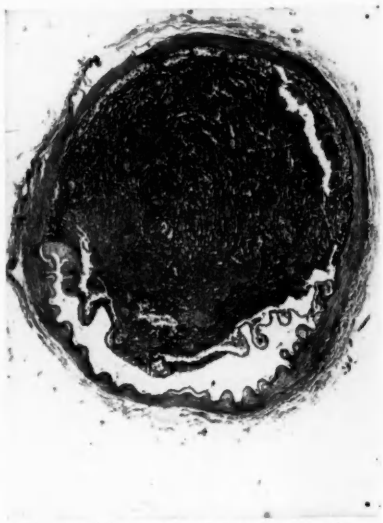

FIG. 2. (*Case 1*).—Transverse section of right middle cerebral artery showing lumen displaced to one side by a thrombus in the wall between the media and internal elastic lamina. Elastic Masson Stain. × 26.

FIG. 3. (*Case 1.*)—Transverse section of terminal part of right internal carotid artery showing commencement of dissecting aneurysm at the site of a congenital defect in the media. Elastic Masson Stain. × 20.

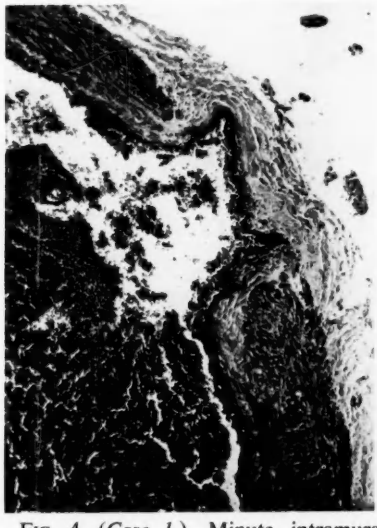

FIG. 4. (*Case 1.*)—Minute intramural aneurysm at the bifurcation of the terminal part of the right internal carotid artery. It is lined by internal elastic lamina which terminates abruptly on one side. Elastic Masson Stain. × 53.

To illustrate article by Lionel Wolman.

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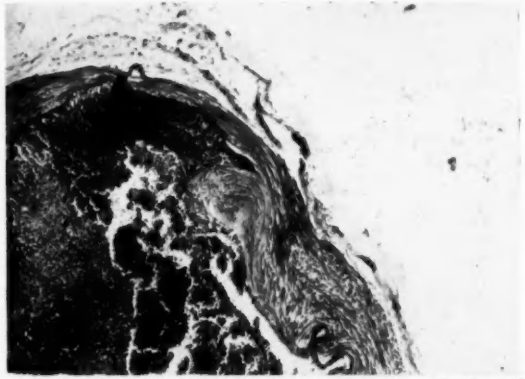

FIG. 5 (*Case 1*).—Site of commencement of dissection between the frayed internal elastic lamina and media in the proximal part of right middle cerebral artery. Elastic Masson Stain. × 53.

FIG. 6 (*Case 2*).—Left hemispherectomy showing atrophic area in the territory supplied by the middle cerebral artery.

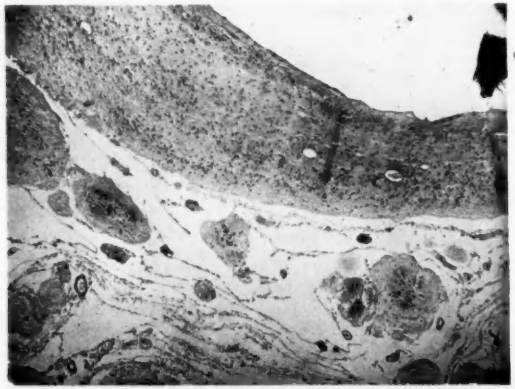

FIG. 7 (*Case 2*).—Thin densely gliosed wall of dilated lateral ventricle in atrophic zone with glial nodules in pia arachnoid. Hæmatoxylin and eosin. × 45.

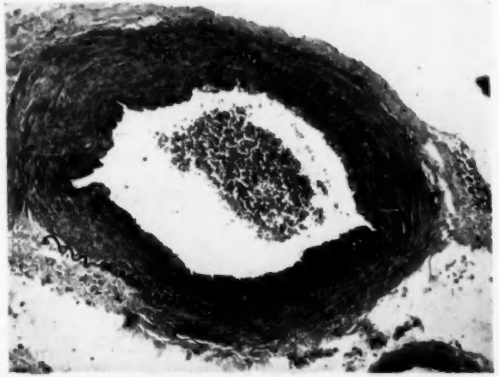

FIG. 8 (*Case 2*).—Proximal part of left middle cerebral artery showing congenital defect in the media with disappearance of the internal elastic lamina over a large segment. A second muscle coat and elastic lamina are present internal to these and surround the lumen. Elastic Masson Stain. × 20.

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To illustrate article by Lionel Wolman.

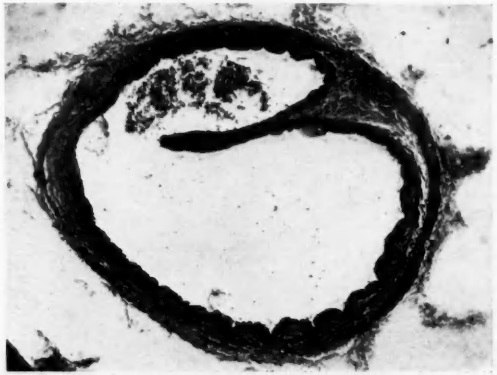

FIG. 9 (*Case 2*).—Transverse section of left middle cerebral artery at its first bifurcation showing original lumen displaced to one side and obliterated by fibrous tissue. Elastic Masson Stain. × 20.

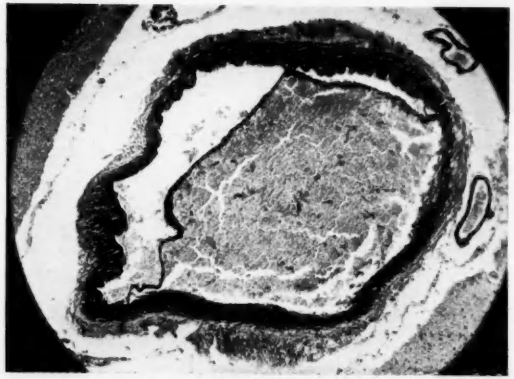

FIG. 10 (*Case 3*).—Transverse section of left posterior cerebral artery showing dissecting aneurysm. Elastic Masson Stain. × 38.

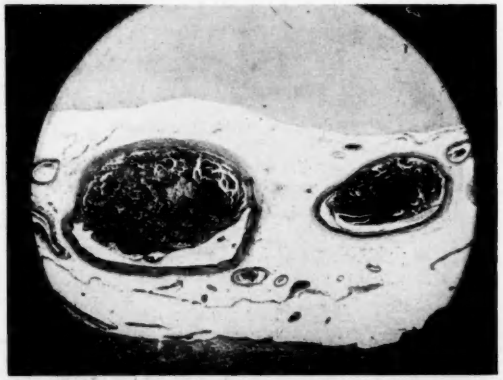

FIG. 11 (*Case 3*).—Transverse section of right posterior cerebral artery and one of its branches showing thrombus in the wall narrowing the lumen. Elastic Masson Stain. × 38.

FIG. 12 (*Case 3*).—Transverse section of upper part of basilar artery showing dissecting aneurysm. Elastic Masson Stain. × 38.

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NOTICES OF RECENT PUBLICATIONS

A PHILOSOPHY OF PERCEPTION

The Nature of Experience. Riddell Memorial Lectures. Thirtieth Series. By Sir Russell Brain, Bt. 1959. Pp. 73. Oxford University Press. Price 8s. 6d.

These lectures are an extension of the author's previous work, "Mind, Perception and Science," Oxford 1951, which suggested some very interesting answers to an ancient philosophical problem. Galileo, Locke and their successors have taught that external objects are merely masses in motion and that their apparent colours, sounds and smells are actually not theirs, but are generated in us by the impact of external objects on our eyes, ears and noses. Modern neurology has borne out the belief in the internal location of colours, sounds and smells, by proving that they can be produced internally as after-images, illusions or hallucinations. And it has gone well beyond this, by tracing the neural processes which conduct the external impact to the cerebral cortex and identifying the several cortical centres which produce our awareness of sights, sounds and smells. Modern knowledge has thus added compulsive force to the philosophical problem which Sir Russell takes up here, namely: How do we come to know external objects, if our awareness of them is altogether internal?

The author sets out by opposing the view current among the analytical philosophers whose influence predominates in England today, that the problem can be eliminated by a more careful use of terms. Analytical philosophers can admittedly show a strong prima facie case for assuming some verbal confusion by pointing out that the alleged problem involves a self-contradiction. For the questioning of all external observation is itself based on external observations: it assumes certain observations of physics and neurology to be valid. I do not think that Sir Russell denies this self-contradiction, but he rejects the analytical remedy offered for it. This remedy amounts to restricting the applicability of terms like "seeing," "hearing," "smelling" to the sights, sounds and smells experienced by the speaker, entirely disregarding in this connexion any knowledge of the neural and cortical processes which underlie these experiences. Illusions, hallucinations and other internally produced seeings, hearings or smellings are then taken into account by admitting that further seeing, hearing, etc., may occasionally show that previous seeing, hearing, etc., was erroneous.

Sir Russell rejects this conception of sensory experiences, since it achieves self-consistency only by ignoring the physiological basis of such experiences. He wants us to comprehend jointly both our perceptions and the neural processes that underlie them. His first step in this direction is perhaps his most ingenious and original contribution—but it is at the same time a concession to the analytical point of view. It consists in extending "sensory experience" to include our awareness of externality. It follows then that "We do not need to ask how we become aware of things outside ourselves because it is with that awareness that we begin." This formulation accepts our immediate experience of external objects, as the analytical school does, and yet retains the internal location of this experience by equating it with the sights, sounds and other awarenesses produced by neural processes.

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Of course there are difficulties attached to this advantage. The sights, sounds, etc., are now placed inside the brain, and to make room for them the author (following Lord Russell) has to postulate a private perceptual space as distinct from the physical space in which the brain itself is located. Then another new hypothesis, linked to the conception of directly observed externality, is needed to bridge the fateful gap between sensory experiences inside the brain and the knowledge of external objects to which they refer. Sensory qualities are said to be experienced, not in themselves, but as symbols by which we become aware of external objects with their corresponding qualities of colour, sound, smell, etc. Sensory experiences are compared to the pictures on a radar screen by which we see approaching objects and are guided in dealing with them.

A distinct advance has been achieved here; but I feel that it does not go far enough. Can we speak of symbols without identifying the person to whom they signify something, the person who means something by them? Sir Russell speaks of "my knowledge" or of "my brain." I suggest that this indicates the missing personal centre. It is not my spectacles that see this table, not my eyes, not the afferent neural processes, nor is it the cortex of my brain, but it is *I* who see the table by the aid of these instruments of my perception.

I believe that Sir Russell cannot avoid the admission of my person once he speaks of my sense experiences as symbols, and I suggest that once he does admit my person there is no need to postulate sense data localized in my brain. He can speak then instead of my awareness of neural processes within my body in terms of the corresponding sensory qualities of external objects.

I believe also that this alone can eliminate a grave difficulty in the conception of sense data. What of the opening of my pupils and the contraction of my eye muscles? Are they sense data? We are not aware of these reflex actions in themselves, yet they function as symbols in Sir Russell's sense in so far as they are factors in determining the place where and the size in which we see an object. Actually, we are aware of these muscular processes only in terms of external knowledge, exactly as we are aware of the appropriate cortical processes; the former should, therefore, be classed with the latter as tools of or clues to perception.

This is not to dismiss "sense data." They should be recognized in the meaningless fragments of a puzzling sight. The effort to make out a camouflaged object leads from the experience of sense data to the perception of an object. But for this definition of sense data we must again admit the presence of an active mind who is striving to make sense of them.

It all leads up to the old question whether all mental actions can be represented by a neural automaton. I believe that Sir Russell's stimulating reconsideration of perception can be completed only by the rejection of automatism and the admission of an active centre of personal judgment.

MICHAEL POLANYI.

PSYCHOMETRIC TESTS

Manuel pratigue du Test de Rorschach. By M. LOOSLI-USTERI. Pp. 216. Paris: Hermann. Price 1,680 Fr.

Perceptual Processes and Mental Illness. By H. J. EYSENCK, G. W. GANGER, J. C. BRENGELMANN. Pp. 144. London: Chapman and Hall. Price 25s.

Diagnostic Performance Tests. By B. SEMEONOFF and E. TRIST. Pp. 176. London: Tavistock Publications. Price 32s.

The same idea underlies these three books—that differences in personality may be manifest in differences in more fundamental perceptual and motor processes—but

the methods by which the authors proceed are entirely different. Dr. Loosli-Usteri quotes with approval the dictum of Binder, that the Rorschach test is "a magic mirror of the inner soul," and presents an extended discussion of the usual arbitrary "signs." It is encouraging to note that she derives the signs of normality from a statistical analysis of groups of normal subjects; but the validity of the signs in psychiatric diagnosis is not examined with the same thoroughness.

For Professor Eysenck, on the other hand, there is no virtue in a test unless the results discriminate to a statistically significant degree between patients and normal controls. He and his co-workers present statistical analyses of results on 76 tests, ranging from questionnaires and intelligence tests to simple perceptual and motor situations. Some results discriminate; others do not; and yet others discriminate in an unexpected direction. The analysis does not contribute to our understanding of the processes underlying mental disease, but it gives Prof. Eysenck an opportunity, in the last paragraph, to tilt at his favourite windmill, the "dynamic" schools of psychopathology.

The study of Dr. Semeonoff and Mr. Trist is informed by a more realistic approach. The paragraphs on pp. 2–3 are a particularly clear statement of the importance of flexibility when administering standardized tests to patients; it is odd, in contrast, to see the tester's stopwatch so prominently displayed in the photographs. There follows a detailed description of the ways in which features of personality may be reflected in the qualitative manner of performance of a number of tests; but the final analysis is concerned only with test scores, and does not present any conclusive evidence in favour of the validity of the qualitative signs. At present, it cannot be claimed that any psychological test, other than those of intellectual function, is of either clinical or theoretical value in psychiatry.

JOHN McFIE.

RADIOACTIVE ISOTOPES

External Collimation Detection of Intracranial Neoplasia with Unstable Nuclides. By G. M. Shy, R. B. Bradley and W. B. Matthews. 1958. Pp. 144. Edinburgh and London: E. & S. Livingstone Ltd. Price £1 10s. 0d.

Artificial radioactive isotopes have found an increasing number of applications in clinical investigation and diagnosis. For example, studies of normal and abnormal metabolic processes difficult to investigate by other techniques can relatively simply be made with them. In one field of possible development, however, the detection and localization of malignant growth, the results achieved seldom reflect the effort expended.

In the method which forms the subject of this book, a suitable γ-ray emitting radioactive material is given to the patient. Then γ-ray counters are used to try to detect regions of relatively high concentration of radioactivity which may be the sites of neoplasia. As a result of the unique power of thyroid tissue to concentrate iodine such a technique is widely and successfully used for the investigation of metastatic thyroid carcinoma: radioactive iodine concentrations in functioning metastases may be several hundred times those in other tissues of the body and the relative ease with which such metastases may be detected is shown by one series of illustrations in the present book. In general the concentrations of any radioactively labelled substance so far tested in brain tumours, relative to those in surrounding normal tissues, are comparatively small so that the method is likely to be less accurate than well-established X-ray diagnostic techniques. It is now some ten years since the first attempts were made to localize brain tumours in this way and it would be interesting to have a detailed survey of the progress achieved. However, after a brief historical introduction, the authors of this book confine themselves almost entirely to an account

of the elaborate equipment developed a few years ago at their institution and to a discussion of the results of their investigations of 179 patients, using as tracer iodine-131 labelled human serum albumin.

In their equipment they use as γ-ray detectors a pair of large scintillation crystals, fitted with massive lead or gold collimators and mounted in automatic scanning apparatus. A full description of the measurement technique is given, and the results of their clinical work are analysed in some detail. The authors stress that, as a result of the relatively high uptake of the labelled albumin in normal tissues, it is necessary to treat the problem radiographically, abnormality being superimposed on a distinctive normal pattern of counts. The importance of experience in interpreting the results will be evident on examination of many of the illustrations of scans made with their equipment. In discussion, the authors point out that the accuracy obtained approaches that found in air studies, yet involves the patient in minimum hazard. Whilst this conclusion may be accepted it seems probable that, despite the elegance of the physical technique neither further advance nor a wide adoption of the method can be expected unless some means can be found of achieving a higher preferential uptake of a suitable radioactive substance in the tumour itself.

The book has 15 chapters and more than 100 illustrations. It is well produced and contains much original material. It may be welcomed as an interesting specialized monograph on a tantalizingly difficult diagnostic technique.

N. G. TROTT.

LIVER-BRAIN RELATIONSHIPS

Liver-Brain Relationships. By IAN A. BROWN, M.D., Ph.D., Asst. Prof. in Neurology, University Minnesota. Pp. 198. Chicago: Charles C. Thomas. Price 50s.

This volume deals with a subject about which there is at present much speculation and considerable research. Modern concepts of many diseases are biochemically inclined and the author of this monograph on the liver-brain relationships in his conclusions says that it is hoped that the era of the light microscope is ended and that the future lies in intensive biochemical study.

The material for the book is derived from a study of 42 patients with hepatic disease and coma, and 40 patients with liver disorder but without coma, seen before 1954. Many of his observations are tabulated rather than fully discussed. Relevant —and sometimes irrelevant—facts from large numbers of research workers are mentioned, but not always critically considered in relation to the results he found in his patients clinically, biochemically and histologically.

There is some lack of uniformity of the spelling of names and of some chemical substances, and a few of the references show minor errors.

However, the volume makes interesting reading and gathers together most of the information available, and it is well produced.

J. N. CUMINGS.

SOLVITUR AMBULANDO

Therapeutic Exercise. Edited by SYDNEY LICHT. Pp. 893. Elizabeth Licht, Publisher. New Haven. Price $16.

This book is designed to cover the entire range of medical gymnastics, but, being the work of no less than 36 authors, and priced at 16 dollars, it is not likely to appeal to neurologists in this country. Apart from Coërs' chapter on the structure of the motor unit, fundamental neuro-physiological problems concerning stance and motion are scarcely touched upon. Kabat's chapter on proprioceptive facilitation, and Wynn Parry's on trick movements are full of interest, but one cannot help feeling that fewer writers would have made a more homogeneous and instructive volume. Thus,

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movements of the upper and lower limbs are described by different authors, while a third deals with the mechanics of movement of posture, and yet there is no reference in the index to "standing" as such. Readers of this Journal will draw their own conclusion from the omission of any mention of Beevor in the chapters on movement and on hemiplegia. Oddities of language like "physiatrist" and "ambulatory training" cannot be ascribed only to the American contributors, for Professor MacConaill's entertaining chapter puts forward his classification of muscles into "spurt" and "shunt" muscles; so perhaps in objecting to these terms one merely emphasizes one's own insularity. This book has been designed for specialists in physical medicine, and physiotherapists. Quite properly many chapters are concerned with equipment, and one chapter has been devoted entirely to the walking stick. While every possible advice is given in the correct method of standing in crutches, one looks in vain for a lucid account of how one stands up without them.

JOHN FOLEY.

SHORTER NOTICES

A History of Neurology. By WALTHER RIESE, M.D., Associate Professor of Psychiatry and Neurology; Associate Professor of the History of Medicine, Chairman of the Department of the History of Medicine, Medical College of Virginia, Richmond, Virginia. 1959. Pp. 223, 4 figures. New York: M.D. Publications Inc. Price $4.00.

It is inaccurate to call this book "A History of Neurology," since it is mostly concerned with the development of a certain holistic and dynamic theory of the functions of the nervous system. The author gives a sound historical account of the evolution of the basic concepts of nervous function, such as the nervous impulse, reflex action and the doctrine of cerebral localization. He then acclaims "the rediscovery of the whole." The two concluding chapters deal in twelve pages with the history of neurological diagnosis and prognosis: only the briefest references are made to neuropathology. Some lack of proportion is evident in a "history of neurology" which gives 26 references to Hughlings Jackson and only six lines of text to Sherrington, and fails to mention Gowers and Holmes, even in the concluding calendar of neurological saints which begins with Galen and ends with Wilder Penfield and Sir Frances [*sic*] Walshe.

Grosse Nervenarzte. Band 2. Edited by KURT KOLLE. 1959. Pp. 251. 24 illustrations. Stuttgart: Georg Thieme Verlag. Price DM. 29.40.

This is the second volume, in German, of biographies of famous neurologists, neurosurgeons and psychiatrists, and deals with 22 more personalities—amongst them Nissl, Alzheimer, Wernicke, Adolf Meyer, Pierre Marie, Babinski, Head, von Economo, Horsley and Dandy. The English contributors are Macdonald Critchley on Head, and Sir Geoffrey Jefferson on Horsley. There is also an article by E. H. Ackerknecht on the history of institutions devoted to neurology and psychiatry in non-German-speaking European countries.

Epilepsy Handbook. By FREDERICK A. GIBBS and FREDERICK W. STAMPS. Pp. 101. Oxford: Blackwell. Price 36s.

This is a good potted guide for the family doctor, tiny and tremendously expensive.

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